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FACTORS INFLUENCING ADRENOCORTICAL ACTIVITY IN HEALTH AND DISEASE*

BY

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The heightened interest in the adrenal cortex and its secretory products over the last few years is largely due to two factors—the belief by some workers that several diseases of unknown aetiology, such as rheumatoid arthritis, are caused by an imbalance in the various hormones secreted by the adrenal gland, and the advent of pure adrenal steroids and corticotrophin (A.C.T.H.) in sufficient amounts for use in clinical medicine. There can be no doubt that these agents are of considerable value in the treatment of certain diseases, particularly in the control of status asthmaticus and rheumatoid arthritis, and also in testing adrenocortical function so that the diagnosis of certain endocrine diseases can be more accurate and founded on a truly scientific basis. The proper use of these agents requires some knowledge of the mechanism by which they and other factors influence adrenocortical function.

The many different hormones secreted by the cells of the suprarenal cortex can be classified under five main headings according to their chief physiological actions. These five categories comprise glucocorticoids, androgenic steroids, mineralocorticosteroids, oestrogenic steroids, and progestational steroids: very little is known about the last two groups, and they are not discussed further. These subdivisions are somewhat arbitrary, because the actions of these hormones often overlap. For example, glucocorticoids, which include such compounds as hydrocortisone (also known as cortisol and compound F) and corticosterone (Albright calls them the "S" or sugar hormones because of their influence on carbohydrate metabolism), not only affect protein, carbohydrate, and fat metabolism but influence salt and water metabolism as well. There is evidence, however, for a specific mineralocorticoid which controls salt and water metabolism—namely, aldosterone, a hormone recently isolated by Simpson *et al.* (1954). Little is yet known about its role in health and disease, although there is enough evidence to indicate that the factors which control its secretion are different from those which promote the formation of hydrocortisone (Simpson and Tait, personal communication; Prunty *et al.*, 1954). Androgenic steroids, which Albright has called the "N" or nitrogen-retaining hormones because of their ability to promote anabolism of protein in addition to their action on the secondary sexual manifestations, also appear to be controlled to some extent by different factors from those concerned with the formation of glucocorticoids and aldosterone. Thus in considering the factors which influence adrenocortical activity in health and disease it is necessary to define which particular adrenal function is under discussion. This report is concerned chiefly with the secretion of glucocorticoids: our knowledge is far from complete, and in a rapidly developing field of research this is inevitably in the nature of an interim report on work in progress in several different centres.

INDICES OF ADRENOCORTICAL ACTIVITY

Glucocorticoid Secretion

Research into the secretion of corticosteroids has been beset with difficulties largely owing to lack of satisfactory methods. In the past much valuable information has been obtained from animal experiments in which assessment of adrenocortical activity has been based on such indirect indices as the degree of ascorbic acid or cholesterol depletion in the adrenal glands—changes which have been accepted as evidence of increased secretion of corticosteroids. However, the significance of these changes is still uncertain, and in endocrinology, perhaps more than in any other subject, it is unwise to translate from animal experiments to man. In man, too, indirect indices of adrenocortical activity have been used. Some of these, such as the fall in eosinophils, have proved under certain circumstances to be misleading. The significance of these eosinophil changes is discussed later.

More direct assessment of adrenocortical function is obtained by measuring the concentration of corticosteroids in the blood and in the urine. In principle the technique of estimating plasma corticosteroids is simple. A sample of 15 ml. of plasma is extracted with chloroform. The extract is dried and then purified by column chromatography. The steroids are estimated by a colour reaction with phenylhydrazine in sulphuric acid which is specific for C-17 dihydroxy-ketones (Porter and Silber, 1950; Nelson and Samuels, 1952; Bayliss and Steinbeck, 1953). By working up large volumes of fresh plasma it has been found that the bulk of the material measured is hydrocortisone (Nelson and Samuels, 1952), although some of the colour is produced by metabolites such as tetrahydrocortisone (Bayliss and Steinbeck, 1953; unpublished observations). The identification of the compounds present has been made by paper chromatography, eluting the steroids off the

*A lecture given to the Postgraduate Medical School and the Institute of the British Postgraduate Medical Federation as part of the course on "The Scientific Basis of Medicine." Delivered at the London School of Hygiene and Tropical Medicine on November 25, 1954.

paper and then recording the characteristic absorption spectra they give when reacted with concentrated sulphuric acid (Zaffaroni, 1950, 1953).

There are certain shortcomings in using the plasma concentration of 17-hydroxycorticosteroids as an index of adrenocortical activity. First, the method does not measure corticosterone, which is a normal, but probably not a major, constituent of adrenocortical secretion. The second, and in this context the more important, shortcoming is that the concentration of 17-hydroxycorticosteroids in the plasma may not necessarily be an index of adrenal activity. The level in the plasma is

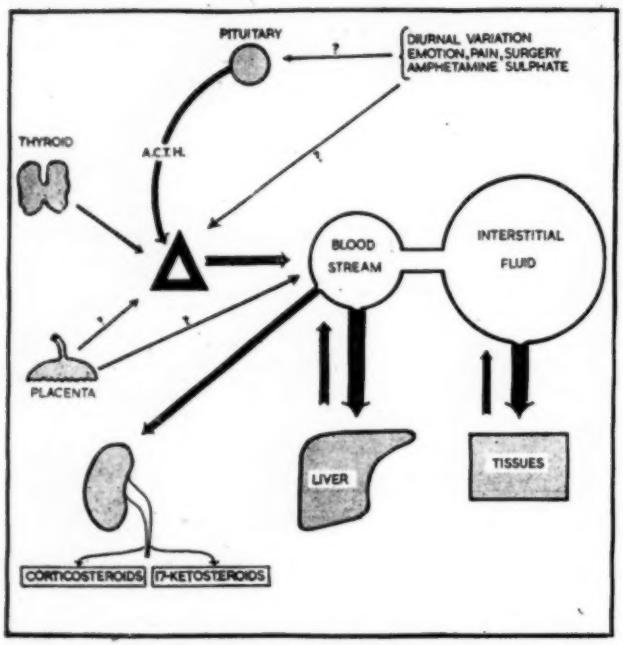

Diagram to illustrate some of the factors which influence the plasma level of 17-hydroxycorticosteroids.

the resultant of several factors (see Diagram)—the quantity being secreted by the adrenal glands, the quantity being metabolized and utilized in the tissues, and the quantity being excreted in the faeces and urine.

Secretion

Steroids secreted by the adrenal cortex pass into the blood stream and thence into the extracellular fluid. Paper chromatographic analysis of fluid removed from the pleural space or peritoneal cavity has shown the presence of hydrocortisone and also, in some specimens, very small amounts of tetrahydrocortisone (Cope and Hurlock, 1953, 1954). The 17-hydroxycorticosteroid content of pleural and ascitic fluid is of the same order as that found in blood samples, and this suggests that adrenocortical hormones diffuse readily from the vascular into the interstitial fluid compartments (Bayliss and Steinbeck, unpublished observations).

Utilization

Adrenocortical steroids are metabolized in the tissues and particularly in the liver. In the dog there is a considerable steroid gradient across the liver, and after giving cortisone by mouth the steroid concentration is much higher in the portal venous blood than in blood from the hepatic vein (Bayliss *et al.*, 1954b). In man a dose of 50 mg. of cortisone by mouth causes a rapid increase in the plasma steroid level, but the hormone disappears quickly from the blood stream and the plasma level returns to normal in four to six hours (Bayliss and Steinbeck, 1955).

Little is known of the metabolism of corticosteroids in peripheral tissues. Nelson *et al.* (1951) failed to find a significant arteriovenous difference across the limbs. This is perhaps not surprising, since Louchart and Jailer (1952) found that little disappeared when cortisone was incubated with slices of muscle or brain, but that large losses occurred in the presence of liver, kidney, or spleen slices. On the other hand, when hydrocortisone or cortisone is injected into a knee-joint the steroid is rapidly metabolized, and if some of the joint fluid is withdrawn half an hour later the hormone has been converted into other compounds (Wilson *et al.*, 1953).

It is possible that certain substances may interfere with the metabolism of cortisone or hydrocortisone. It was first observed in Holland that patients taking large amounts of liquorice were liable to develop oedema and hypertension (Borst, 1950). It was suggested that glycyrrhetinic acid, believed to be the active ingredient of the liquorice, exerted an effect similar to that of adrenocortical hormones, and that this might be the unwitting reason why salt-depleted miners in certain French coalfields sucked sticks of liquorice at the end of their day's work, just as British miners may add extra salt to their beer. When glycyrrhetinic acid was given to Addisonian patients conflicting results were obtained. Some patients showed clinical improvement and maintained their salt balance (Groen *et al.*, 1951; Card *et al.*, 1953); others did not (Borst *et al.*, 1953). It was observed that when an Addisonian patient was given cortisone a smaller dose combined with glycyrrhetinic acid produced the same therapeutic effect as a larger dose given alone. This suggests that liquorice may act by blocking the enzyme systems which metabolize corticosteroids. If in an Addisonian patient there is some residual adrenal function and small amounts of steroid are being secreted, glycyrrhetinic acid causes clinical improvement by preventing enzymic breakdown of the adrenal steroids; if, on the other hand, adrenal atrophy is complete and no steroids are being secreted, glycyrrhetinic acid has no effect. Proof of this hypothesis has not yet been obtained.

Urinary Excretion

Although studies with C^{14}-labelled cortisone have shown that eventually about 80% of the radioactivity is eliminated in the urine, much of this material is probably no longer steroidal, because only 5 to 10% of a 50-mg. dose of cortisone is recovered in the urine as corticosteroids and an even smaller amount as neutral 17-ketosteroids. The quantitative estimation of urinary corticosteroids has proved difficult, because the hormones and their metabolites are excreted partly as free compounds and partly as conjugates. The difficulty has been to hydrolyse the conjugated compounds. The method evolved by Norymberski *et al.* (1953) circumvents this difficulty and is likely to prove a most valuable tool in the study of adrenocortical function. The method of Reddy *et al.* (1952) is also promising: it has the great merit of simplicity, but its accuracy has still to be proved. By estimating the 17-hydroxycorticosteroid concentration in plasma and urine the renal clearance of corticosteroids has been measured in the same way as the clearance of urea or creatinine is measured. About 1 ml. or less of plasma is cleared of 17-hydroxycorticosteroids per minute. Since data from studying the steroid concentration in ascitic and pleural fluid indicate that these hormones are diffusible, the low clearance must be due to active reabsorption in the tubular lumen, which is the method used for conserving substances important to the body economy.

These, then, are some of the factors which may influence the concentration of 17-hydroxycorticosteroids in the plasma.

In normal healthy subjects the plasma steroid level ranges from 3 to 17 μg. per 100 ml., with a mean of 9 μg. per 100 ml. It is necessary to point out, however, that isolated single determinations may be misleading, because there is evidence, discussed below, that emotional factors

may influence plasma steroid concentration and high values may occur in normal people during an emotional disturbance.

Androgenic Steroid Secretion

The urinary excretion of neutral 17-ketosteroids is generally accepted as an index of androgenic steroid formation in the body. The daily output in the adult male is on the average some 5 mg. higher than in the female—this amount being contributed by androgens of testicular origin. Unfortunately, hydrocortisone and cortisone are in part excreted as 17-ketosteroids, and the total excretion of 17-ketosteroids—derived from both corticosteroids and androgenic steroids and probably other precursors as well—is an imperfect index of androgenic hormone formation. By more complicated chromatographic techniques it is possible to separate 17-ketosteroids into several constituent fractions and determine how much of the total has been derived from corticosteroids and how much from androgenic hormones and other precursors (Dingemanse *et al.*, 1952; Kellie, 1953; Lakshmanan, 1954).

FACTORS INFLUENCING CORTICOSTEROID SECRETION

Corticotrophin

The pituitary trophic hormone A.C.T.H. is the principal factor directly regulating the secretion of corticosteroids (Sayers and Sayers, 1948; Sayers, 1950; Long, 1952). Whether corticotrophin is a protein or a polypeptide, and whether it is one hormone or several, is still undecided (Astwood *et al.*, 1952; Stack-Dunne, 1953; Forsham, 1955), nor is the mechanism by which it increases corticosteroid secretion fully understood. Perfusion studies of ox adrenal glands, carried out at the Worcester Foundation over a number of years, indicate that its action is to accelerate the early stages in the biosynthesis of hydrocortisone and corticosterone from cholesterol and acetate precursors (Pincus, 1954).

The degree of increased adrenocortical activity produced by A.C.T.H. is dependent upon two factors—the amount of hormone administered (Bayliss and Steinbeck, 1954a) and the length of time the stimulating action of the hormone is applied (Renold *et al.*, 1952).

If solutions of A.C.T.H. are infused over a constant time, the degree of adrenocortical stimulation produced is directly related to the dose given. Over a 6-hour period as little as 0.25 unit an hour will cause a significant increase in adrenal activity. If this response is plotted against the logarithm of the dose a straight-line relationship is obtained. The slope of the line is rather flat, so that with increasing doses above 2 units an hour there is little further elevation of the plasma steroid concentration, and for practical purposes it can be assumed that 2 units an hour over a six-hour period will cause maximum adrenal stimulation.

The degree of adrenocortical response to a constant dose of A.C.T.H. is directly proportional to the duration of A.C.T.H. administration (Renold *et al.*, 1952). If a single dose of 20 units is injected intravenously the response of the adrenal cortex is often short-lived and evanescent. In contrast the same amount of hormone dissolved in saline and infused over a six- or eight-hour period causes a profound increase in adrenocortical secretion. These differences are due to the rapid destruction of A.C.T.H. in the body (Sayers *et al.*, 1949; Greenspan *et al.*, 1950; Reiss *et al.*, 1951; Pincus *et al.*, 1952). If A.C.T.H. is dissolved in saline and injected intramuscularly it causes a relatively brief increase in plasma 17-hydroxycorticosteroid concentration lasting about four hours. If the same dose is given intramuscularly in a gelatin menstruum, combined with a zinc precipitant or an oxycellulose adsorbant, a more prolonged effect is observed, the vehicle allowing a gradual release of the A.C.T.H. and preventing its destruction at the site of injection (Bayliss and Steinbeck, 1954a; Oudsten *et al.*, 1954; Greene and Vaughan-Morgan, 1954; Ferriman *et al.*, 1954; Gemzell and Franksson, 1953).

The degree of adrenal stimulation obtained from intramuscular A.C.T.H. in saline or a gelatin menstruum is too variable from one patient to another and in the same patient at different times to allow a quantitative assessment of adrenocortical response. In our hands consistent results are observed only when the material is given by intravenous infusion (Bayliss and Steinbeck, 1954a). This has an important clinical application: the testing of adrenocortical function by giving intramuscular A.C.T.H. is meaningful only if a positive response is obtained. If the response is negative no conclusions can be drawn and the trophic hormone should be infused intravenously.

Deficiency of A.C.T.H. secretion due to pituitary destruction leads to adrenocortical atrophy and low plasma 17-hydroxycorticosteroid levels. The degree of adrenal atrophy is related to the degree of A.C.T.H. deficiency and this in turn to the degree of pituitary destruction. When pituitary destruction is total, or nearly so, the plasma level of 17-hydroxycorticosteroids may fall to zero, and such values are found in patients with gonadal, thyroid, and adrenal failure who require substitution therapy to remain alive. In others in whom the degree of pituitary destruction is less complete and the clinical features indicate only gonadal failure the plasma steroid levels are within the normal range.

Responsiveness of the Adrenal Gland

The amount of steroid secreted by the adrenal cortex depends not only on the degree of stimulation provided by A.C.T.H. but also on the responsiveness of the gland itself. In normal subjects a continuous infusion of A.C.T.H. calls forth a rapid response, which can be detected in the peripheral blood within 15 to 30 minutes of starting the infusion. After reaching a maximum in about an hour, the plasma steroid level remains relatively constant during the remainder of a six- or eight-hour infusion. When the infusion is stopped the increased adrenocortical activity ceases, and within two to three hours the plasma steroid level has returned towards the pre-infusion level. In normal subjects the level attained six to eight hours after starting an A.C.T.H. infusion at the rate of 2 units an hour is usually of the order of 25–35 μg. per 100 ml.—that is, 15 μg. or more above the pre-infusion level. As would be expected, repeated daily infusions cause progressively higher levels, and this suggests that the anatomical hypertrophy of the gland found after repeated infusions is associated with increased functional capacity and heightened steroidogenesis.

Some idea of the total steroid output from adrenal glands receiving maximum stimulation with A.C.T.H. is given by some studies made by Thorn *et al.* (1953). They observed the changes in urinary corticosteroid excretion, eosinophils, electrolyte, and blood glucose concentrations during a four-hour infusion of 3 units of A.C.T.H. an hour and found that quantitatively similar effects were produced in the same subject by infusing 12 mg. of hydrocortisone an hour. From this it may be tentatively inferred that under maximum stimulation the adrenal glands secrete the equivalent of about 300 mg. of compound F per 24 hours.

Addison's Disease

Decreased responsiveness of the adrenal cortex to A.C.T.H. is seen characteristically and diagnostically in Addison's disease. None of the patients we have studied has shown a significant increase in the plasma level after A.C.T.H. infusion. Even those who appear to have some slight residual adrenal function, as evidenced by their symptomatic independence of substitution hormone therapy and by the low but not negligible plasma steroid levels, show no response, and in them the steroid level may actually fall during the infusion, owing perhaps to utilization of the small amount of circulating hormone during

the stress of the procedure. Normal subjects infused with saline alone show little variation in their plasma steroid level, and if during this time there is increased steroid utilization a constant level is maintained by increased A.C.T.H. secretion and increased corticosteroid output. It is tempting to believe that in Addisonian patients with low normal plasma steroid levels, the few remaining adrenocortical cells are responding to their uttermost to large amounts of endogenously produced A.C.T.H. and no further response is possible to exogenous A.C.T.H.

Hypopituitarism

In patients with hypopituitarism the responsiveness of the adrenal glands is often less than in normal subjects, and there is evidence that the degree of responsiveness is related to the duration of the adrenal atrophy. Thus a patient, who was known to have had hypopituitarism for many years following implantation of radon seeds into the sella turcica, and then surgical extirpation of the remaining hypophysial tissue, showed a rise from 0 μg. per 100 ml. to only 6 μg. after a six-hour infusion of A.C.T.H., whereas in a patient who had only recently been hypophysectomized the level rose from zero to 36 μg.; this large increment may indicate, as occurs in animals, that shortly after hypophysectomy the target gland has a heightened response to its trophic hormone.

Adrenogenital Syndrome

In Addison's disease the activity of the adrenal cortex is impaired in all its functions and the formation of glucocorticoids, mineralocorticoids, and androgens is much reduced or absent. In contrast the adrenal glands of patients with virilization due to congenital adrenal hyperplasia have a more isolated defect which is limited to the biosynthesis of glucocorticoids, and in rare instances the mineralocorticoids as well. In most of these patients the circulating level of 17-hydroxycorticosteroids is abnormally low and there is little or no increase following stimulation with A.C.T.H., whereas the formation of androgens, as indicated by the urinary excretion of 17-ketosteroids, is increased and raised even further after A.C.T.H. (Kelley *et al.*, 1952; Bayliss *et al.*, 1954a; Bongiovanni *et al.*, 1954).

This condition provides information concerning the mechanism by which pituitary–adrenocortical activity is regulated. The secretion of A.C.T.H. is controlled by the plasma level of circulating glucocorticoids, and if the steroid concentration falls the pituitary secretes more A.C.T.H., thereby stimulating the adrenal cortex to maintain the plasma steroid concentration. Conversely, if the steroid level in the blood rises the activity of the pituitary is depressed and less A.C.T.H. is elaborated. In congenital adrenal hyperplasia it appears that because the biosynthesis of glucocorticoids is defective (probably through lack of a particular enzyme system) and the plasma concentration is low, the pituitary responds by secreting increased amounts of A.C.T.H. The adrenal glands are unable to secrete more glucocorticoids and respond to the A.C.T.H. by hypertrophying and elaborating large amounts of androgens which are responsible for the virilization of the patient and for the increased urinary excretion of 17-ketosteroids (Bartter *et al.*, 1951; Wilkins *et al.*, 1952; Jailer *et al.*, 1952).

The validity of this concept has been confirmed by the observation that if cortisone or hydrocortisone is given to such patients the activity of the pituitary is suppressed, less A.C.T.H. is elaborated, and the adrenal glands no longer secrete such large amounts of androgens (Wilkins *et al.*, 1951, 1952; Gardner and Migeon, 1952; Bayliss *et al.*, 1954a; Jailer *et al.*, 1954). Thus these patients are treated by the administration of cortisone in sufficient amounts to suppress pituitary activity and to reduce the urinary excretion of 17-ketosteroids to normal limits.

Cushing's Syndrome

In contrast to the conditions discussed above, in all of which the formation of glucocorticoids is reduced, Cushing's syndrome is characterized by abnormally high plasma steroid levels, whether the condition is associated with an adenoma of the adrenal cortex, bilateral adrenal hyperplasia, or a carcinoma. If the condition is due to bilateral adrenal hyperplasia an infusion of A.C.T.H. raises the already high steroid level even higher. This finding suggests a possible explanation for the underlying disorder in Cushing's syndrome of this type. Since the plasma level of corticosteroids is abnormally high, it seems probable that the primary defect lies in the pituitary gland itself, which is insensitive to the normal inhibitory influences of large amounts of circulating steroids. It is as though the "thermostatic" mechanism is set at too high a level and pituitary activity is not shut off until abnormally high plasma steroid levels are attained. Proof of this belief must await a reliable method for estimating the A.C.T.H. content of the blood, but it is significant that when hydrocortisone is infused into such patients there is a reduction in the urinary excretion of 17-ketosteroids, suggesting that the exogenously administered hormone raises the plasma level high enough to suppress pituitary activity. This response is not seen if the condition is due to an adrenal adenoma or carcinoma, and so may be of clinical value in determining the pathology of the disease before surgical exploration (Jailer *et al.*, 1954).

Myxoedema

The hormone secreted by the thyroid gland influences the metabolic rate of all tissues, and it might be anticipated that in severe myxoedema the activity of the adrenal cortex would be impaired and the rate of steroidogenesis retarded. However, in many patients with myxoedema the plasma steroid level is within the normal range, although, of course, in the myxoedematous state utilization may be decreased, and the rate of steroidogenesis correspondingly reduced. In a few patients abnormally low levels have been encountered, and these have risen to normal after substitution therapy with thyroid extract or L-thyroxine. In one patient with hypopituitarism characterized by severe secondary myxoedema, the plasma steroid level rose from 1 μg. per 100 ml. to 6 μg. when replacement therapy was given with thyroxine only.

In addition to A.C.T.H. and the state of the adrenal cortex, other factors influence adrenocortical activity. Most of these are still incompletely understood, and it is uncertain whether they exert their effect by direct action on the adrenal cortex, or by way of the hypothalamus and anterior pituitary, or by increasing tissue "utilization" of corticosteroids. Their importance lies in the fact that their influence is difficult to control and they may operate, unknown to the investigator, during physiological studies.

Diurnal Variation

Healthy adults show a diurnal variation in adrenocortical activity. It has been known for many years that the urinary excretion of 17-ketosteroids varies throughout the day (Pincus and Hoagland, 1943), and Thorn (1954) has reported that the urinary excretion of 17-hydroxycorticosteroids also varies over a 24-hour period. Similarly, the plasma steroid level varies: lowest values are found at night, around midnight, and the highest levels occur at about 6 a.m. (Tyler *et al.*, 1954; Bayliss, 1955). This variation persists whether the subject is up and about his daily work or whether he is confined to bed and receiving a constant amount of food every two hours. It is not related to the diurnal variation that occurs in the urinary excretion of water, sodium, and other electrolytes. What controls this diurnal change in activity remains unknown, and many obvious investigations need to be carried out: Is this rhythm reversed in night workers? Does it occur in blind people? What effect on it has a lesion of the hypothalamus? Is it disturbed in patients with psychiatric disorders or with Cushing's syndrome?

Emotional Factors

Emotional factors may influence adrenocortical activity in certain subjects. We first observed this phenonemon in 1952, and have since confirmed that in certain patients anxiety, frustration, and fear may cause a significant increase in the plasma 17-hydroxycorticosteroid concentration. Repeated venepunctures, although not more painful than usual, may activate the adrenal cortex by calling forth an emotional response. In certain subjects, delivering a lecture to a critical audience has a similar effect. It is because of these influences that it is difficult to define normal plasma steroid levels. A blood sample taken at random from an out-patient on his first attendance may give an erroneously high value because the patient may be suffering anxiety and tension at the time. Usually the levels induced by an emotional upset do not exceed 20 μg. per 100 ml. and are not therefore likely to cause confusion in the differential diagnosis of Cushing's syndrome, but in some instances higher levels are observed. In interpreting the results of physiological studies due allowance must be made for these emotionally prompted rises in plasma corticosteroids, and it is necessary to make repeated observations and to use adequate controls to be certain that the responses observed are due to the change in the specific experimental conditions being studied and not to an emotional upset.

Adrenaline

It is not yet known how emotional disturbances influence the plasma steroid level, but release of adrenaline is a possible intermediate mechanism. It has been thought for some time that, because adrenaline causes a fall in circulating eosinophils, directly or indirectly it stimulates the adrenal glands to secrete increased amounts of corticosteroids (Recant *et al.*, 1950). In normal but not in adrenalectomized subjects A.C.T.H. causes a fall in the number of eosinophils (Thorn *et al.*, 1948 ; Forsham *et al.*, 1948), and, since hydrocortisone or cortisone also causes a fall in eosinophils, it has rightly been assumed that the eosinopenia after A.C.T.H. indicates increased secretion of corticosteroids and a rise in the plasma concentration of adrenocortical hormones. It has been found, however, that adrenaline may cause an eosinopenia in patients who have had both adrenal glands removed (Kark and Muehrcke, 1952), and direct measurement of the steroid concentration in the plasma, and the steroid excretion in the urine after a single injection or a prolonged infusion of adrenaline in normal subjects, has failed to show any increase in adrenocortical activity (Sandberg *et al.*, 1953 ; Thorn *et al.*, 1953).

We were impressed that following A.C.T.H. the fall in eosinophils is greatest two to three hours after the maximum plasma steroid concentration has been obtained ; and that following adrenaline the fall in eosinophils is greatest two hours after the injection. Hence it seemed that any increase in plasma steroids should be looked for within the first few minutes of giving the adrenaline. Despite taking multiple samples at this time, Hunter *et al.* (1955) have failed to detect any consistent increase in plasma steroids, and on the present evidence we must conclude that adrenaline does not cause a detectable increase in adrenocortical activity and is not responsible for the increased plasma steroid levels found in emotional disturbances. It must also be concluded that, although an eosinopenia after administration of A.C.T.H. is a valid index of increased adrenocortical activity, this is not necessarily so under other circumstances.

D-Amphetamine Sulphate

Amphetamine sulphate has many of the pharmacological properties of adrenaline, but a more prolonged action. In 1952 a patient with panhypopituitarism due to a large chromophobe adenoma which was also causing attacks of diencephalic epilepsy was found to have plasma corticosteroid levels above normal—22 μg. per 100 ml. This surprising result was obtained at a time when the patient was receiving amphetamine sulphate for his diencephalic epilepsy. When the amphetamine was stopped the plasma steroid level fell to the anticipated low value of 3 μg. per 100 ml. Subsequently Thorn (1954) has noted that some patients have increased urinary excretion of 17-hydroxycorticosteroids following "benzedrine," and we have found similar changes in the plasma steroid levels.

Stress

Selye (1946) has suggested that a wide variety of factors, such as infections, intoxications, trauma, nervous strain, heat, cold, muscular fatigue, and *x*-irradiation induce a state of general systemic stress which is associated with increased adrenocortical activity. Whether or not these many different factors do indeed cause increased cortical secretion remains to be proved. Thorn *et al.* (1953) have not observed an increase in the urinary excretion of 17-hydroxycorticosteroids after physical exertion, exposure to cold, anoxia, or mental exertion involving the use of an Air Force pursuit meter ; but these results cannot yet be accepted with complete confidence because of the analytical method used. Increased steroid excretion was noted in members of the Harvard boat-race crew, but since the cox and the coach showed a similar response the increased adrenocortical activity seemed more attributable to emotional factors than to the physical exertion *per se*. The plasma steroid level shows no consistent change in patients receiving whole-body *x*-irradiation sufficient to cause radiation sickness.

Surgical operations do increase the urinary excretion of corticosteroids (Cope *et al.*, 1951 ; Thorn *et al.*, 1953) and raise plasma steroid levels (Franksson *et al.*, 1954), and increased adrenocortical activity is commonly observed in any painful condition. For example, an elderly patient with severe cephalgia due to temporal and occipital arteritis had consistently high values of 26 μg. per 100 ml., which returned to normal levels when the pain subsided, although the disease continued to be active. Patients with a myocardial infarct may show high levels. One admitted soon after the onset had a level of 50 μg. per 100 ml., which rose to 82 μg. per 100 ml. when she seemed on the point of dying. With recovery the plasma steroid level returned to a normal value of 9 μg. In several patients studied in the terminal stages of their illness very high steroid levels have been observed. This is not necessarily associated with urea retention and therefore is not attributable to failure of renal excretion. These findings may not, however, represent increased adrenocortical secretion : they may indicate failure of tissue utilization or impaired hepatic metabolism.

Salicylates

It has been suggested that salicylates exert their beneficial action in rheumatic affections by increasing adrenocortical activity (Hetzel and Hine, 1951 ; van Cauwenberge and Heusghem, 1951 ; van Cauwenberge and Betz, 1952). However, in ordinary therapeutic dosage salicylates do not cause a significant or constant increase in the plasma level of 17-hydroxycorticosteroids despite symptomatic relief and mild manifestations of salicylism (Bayliss and Steinbeck, 1954b), although poisoning with salicylates has been reported to increase the level (Done *et al.*, 1954).

Pregnancy

As judged by the urinary excretion of corticosteroids, there is evidence that the activity of the adrenal cortex is increased during pregnancy (Venning, 1946 ; Tobian, 1949 ; Cope *et al.*, 1951), and the plasma steroid level is also raised (Gemzell, 1953). Blood samples taken from 30 women at monthly intervals throughout pregnancy show a progressive increase in 17-hydroxycorticosteroids, the mean value for the group rising from 10 to 13 μg. per 100 ml. during the third and fourth months to 24 μg. during the last month. The concentration in blood taken from the umbilical cord

at the time of delivery was of the same order—27 μg. per 100 ml. During the post-partum period the level in the mothers' blood fell, the mean concentration for the group returning to normal by the eighth post-partum day. The levels in individual patients varied considerably from the mean values. About 45% showed a marked increase, with maximum levels exceeding 29 μg. per 100 ml.; another 45% had more moderate increases, with maximum values of more than 21 μg.; and in 10% the level did not exceed 20 μg. per 100 ml. (Bayliss *et al.*, 1955).

One important question which remains unanswered is the origin of this steroidal material. Does it arise in the mother or in the foetus? Since in newborn infants the urinary excretion of 17-ketosteroids, glycogenic corticosteroids, and reducing steroids, and the plasma level of 17-hydroxycorticosteroids are all low (Talbot *et al.*, 1943; Venning *et al.*, 1949; Day, 1948; Klein *et al.*, 1954) whereas the level of plasma 17-hydroxycorticosteroids remains high in the maternal circulation for a week after delivery, it seems probable that the site of origin is in the mother. Here three possible sites need consideration—the adrenal glands, which have an increased weight during pregnancy; the placenta, which is known to form other steroids such as progesterone; and the ovaries. Blood samples taken during caesarean section from a uterine vein or a maternal placental sinus and from a peripheral vein have not shown a significant difference in 17-hydroxycorticosteroid concentration, and if the steroidal material were elaborated mainly in the placenta it would be expected that after delivery the concentration in the mother would fall more rapidly than it does. However, observations made in Addisonian patients who have become pregnant suggest that adrenocortical-like hormones are formed in the placenta (Samuels *et al.*, 1943; Knowlton *et al.*, 1949; Jailer and Knowlton, 1950). There is also evidence that an A.C.T.H.-like hormone is formed in the placenta (Jailer and Knowlton, 1950; Opsahl and Long, 1951; Tarantino, 1951; Cohen and Kleinberg, 1952). Thus it may well be that in pregnancy increased amounts of adrenocortical steroids are formed both in the maternal adrenals and to a lesser extent in the placenta.

Two years ago Professor Long (1952) wrote: "I am of the opinion that the greatest obstacle to our understanding lies in the inadequacy of the methods at present employed for the detection of an increased secretory rate from either the anterior pituitary or adrenal cortex." Although some progress has been made, we are still lacking satisfactory methods, and the secretion of many hormones by the adrenal cortex makes a study of its activity complicated and often laborious. I have dealt with only glucocorticoid secretion and with only some of the factors which influence this particular activity, but enough has been said to indicate the changes that occur through the seven stages of man from the high levels in pregnancy, the low levels in the newborn infant, to again the high levels that may be found at the time of death.

Summary

The adrenal cortex elaborates a large number of different hormones which to some degree overlap in their physiological effects. Current investigations are chiefly concerned with 17-hydroxycorticosteroids (such as cortisone and hydrocortisone), androgenic steroids (as reflected in the urinary excretion of 17-ketosteroids), and in the compound which is probably responsible for the control of salt and water metabolism (aldosterone).

In the work reviewed here adrenocortical activity has been assessed by studying the plasma concentration of 17-hydroxycorticosteroids. The plasma level is influenced by the amount of material secreted by the adrenal glands (which is mainly controlled by the release of A.C.T.H. from the pituitary gland), by the "utilization" of the liberated steroids in the tissues (particularly in the liver), and by the rate of urinary excretion.

The plasma level of 17-hydroxycorticosteroids is the same in both sexes. It shows a diurnal variation, and increased values are found in pregnancy, Cushing's syndrome, certain emotional disturbances, following surgical operations, in painful conditions, and at the time of death. No consistent increase in adrenal activity has been observed after administration of adrenaline, salicylates, or deep *x*-irradiation in ordinary therapeutic dosage. Amphetamine sulphate increases the plasma steroid level in some subjects. The relationship between the adrenal response and the dose of A.C.T.H. and the duration of its administration is discussed.

Low plasma adrenal steroid values are found in Addison's disease (and there is evidence that in these patients adrenocortical failure may be complete or only partial), in patients with extensive pituitary destruction, in congenital adrenal hyperplasia associated with virilism, and in some patients with myxoedema.

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ENDOCRINE TREATMENT IN PSYCHIATRY*

BY

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Endocrine therapy has a definite but restricted place in psychiatric practice; in some conditions its use is accepted, in others presumptive. With a few possible exceptions, such as cretinism, there are no psychiatric disorders in which an endocrine disturbance or deficiency has been proved to be an exclusive or major factor in causation. In contrast to the many papers published on research in the endocrinology of psychiatric illness in recent years, there are few about endocrine therapy and fewer that carry conviction.

Since the ductless glands are essential to adaptation and the preservation of physical and emotional stability, and can be disturbed by psychological upset, it is reasonable that psychiatrists should have looked to the field of endocrine treatment.

Although physiological disturbances and abnormalities of body constitution can be seen in any selection of chronic psychotics, the usual symptomatology of endocrine illnesses is rare in psychiatric disorders. Laboratory methods for investigating ductless gland function which have been evolved up to the present are probably not sufficiently precise or reliable to indicate and guide therapy in the absence of clinical signs of endocrine disease, and are not yet convenient for routine use. Thus endocrine treatment is still empirical, and the attempts to make it rational by laboratory methods have not yet been successful.

*From a Maudsley Bequest Lecture given in London on April 5, 1954.

Endocrine preparations may be used because of their physiological and pharmacological effect or as replacement; probably to some extent both aspects enter into successful therapy. It is improbable that lack of one hormone is responsible for any psychiatric disorder, and a replacement therapy is unlikely to be found.

An endocrine disturbance is only one factor in an illness which can be regarded as a reaction between physical and psychological components; but it may be responsible for great difficulties in adjustment. Endocrine therapy aims at improving this factor, so contributing to the total therapeutic effort by benefiting the adaptive or reactive capacity of the patient. It must be preceded by careful psychiatric assessment and investigation, and accompanied by adequate psychotherapy.

Endocrinology in psychiatry can conveniently be considered from the following aspects: (1) conditions encountered in psychiatric practice for which therapy is no longer experimental; (2) psychiatric aspects of endocrine disorders; and (3) experimental endocrine treatment of the psychoses and psychoneuroses.

Conditions Encountered

The Menopause

The features of menopausal depression, irritability, or neurosis need only be mentioned briefly here. There are few women who do not experience psychological changes during the months or years in which ovarian function is failing. The degree to which a woman is disturbed seems to depend upon her capacity for emotional adjustment, general stability, and reaction to ill-health. Many women who suffer most at the menopause report that they have usually experienced mood swings and physical discomfort at some part of the menstrual cycle. It is not correct to assume that a certain kind of personality suffers at the menopause, or is immune; but unbalanced and especially aggressive females often become unreasonable almost to the point of psychosis both at the menstrual cycle and at the menopause. A gradual menopause produces more discomfort than an abrupt cessation. Vasomotor disturbances and hot flushes correspond closely with mood swings. It is believed that these are due to a dysbalance in the relationship between pituitary-stimulating hormones and the peripheral ovarian hormones that are now failing, which has been suggested by high prolan excretion.

Treatment with synthetic or natural oestrones (stilboestrol, dienoestrol, or oestrone), or, in severe cases, oestroform by injection, in sufficient quantity to control hot flushes, is all that is required for the somatic disturbances, and makes psychotherapy easier. Stilboestrol is toxic to about 20% of women, especially the older; the dose is about 0.1 mg. daily. The usual dose of oestrone is from 0.2 to 1 mg. daily. A severe menopausal disturbance sometimes occurs years after artificial menopause by radium, or after hysterectomy if the ovaries remain; this is to be treated on the same lines as the normal menopause and is mentioned for this reason. Convulsive therapy—so effective in involutional melancholia—often aggravates menopausal depression and is contraindicated in the presence of hot flushes, because of its stimulating effect on anterior pituitary lobe function.

Involutional Melancholia

Unlike the menopausal reaction, this is a true psychotic depression, with ideas of guilt or of incurable illness, much agitation, and a marked tendency to suicide. It rarely follows a gradual menopause with vasomotor disturbances, and it usually occurs a year or more after sudden cessation of menses. The pre-psychotic personality is conscientious and inflexible, in contrast to the lability of the menopausal reaction. There is often an appearance of rapid physical ageing, and in some cases there seems to be an anterior pituitary insufficiency, which may be benefited by treatment

with A.C.T.H. But, normally, E.C.T. is the treatment of choice. Experience suggests that oestrones are ineffective, or even contraindicated, as they may suppress anterior pituitary activity.

Pre-menstrual Tension

This term indicates a state of mental and physical tension occurring towards the latter half of the menstrual cycle and prominent about a week before menstruation. The current view is that it is due to water retention produced by abnormal elevation of the oestradiol/progesterone ratio (Rees, 1953; Malleson, 1953).

The diagnosis is made on the occurrence of irritability, emotionalism (even unreasonable aggression), mental discomfort, lack of concentration, coupled with physical discomfort, such as a sense of being blown out, a gain in weight, discomfort in the fit of clothes—due presumably to localized adiposity or water retention. There are occasionally attacks of migraine, or of epilepsy in epileptic subjects.

The usual treatment is ammonium nitrate or ammonium chloride in coated tablets, 0.5 to 1 g. thrice daily for 10 to 12 days before the onset of menses. If this is unsuccessful, progesterone injections, 25 mg. twice daily, or ethisterone tablets, 5 to 20 mg. orally, daily or twice daily. Methyltestosterone, 10 mg. daily, is said to be effective, but may cause virilization.

Assuming that the condition is due to endocrine dysbalance, normal regulation may be established in a few months, when treatment can be discontinued.

Abnormal Libido

Impotence.—This is the inability to perform or complete the sexual act in a male. It may be caused by conditions such as hypogonadism and intersexuality; but usually the external genitalia are normal and the impotence is of psychological origin. This is rarely benefited by endocrine therapy, except where it accompanies the male climacteric or depression, or where it is intermittent and has not existed for long. In long-standing cases of psychological impotence, the interest has been displaced from the sexual object to anxiety whether the act can be performed, causing extinction of the sexual stimulus. Where impotence has occurred in a setting of exhaustion or business worries and has not been prolonged, and where there has not been much controversy between husband and wife, testosterone may improve the sense of well-being, increase libido, and, by making one or two performances possible, improve self-confidence so that anxiety disappears. It is best administered by injection—25 mg. of testosterone propionate three times weekly for a month; oral administration of methyltestosterone is insufficient. Treatment should be discontinued after a fortnight if there has been no response. The patient should not be led to believe it will produce a cure, lest it should not be successful. Intensive psychotherapy is essential. It is unwise to attempt treatment with testosterone in long-standing cases, because of the worsening effects produced by disappointment, as it will certainly fail.

Frigidity.—The diagnosis of frigidity is obviously difficult to make, and the term is a relative one. However, loss of sexual desire or enjoyment is not uncommonly complained of by married women, especially after childbirth; and it has been claimed that treatment with small doses of either oestrone or testosterone improves the appreciation of physical sexual stimuli and will therefore reduce temporary frigidity. Testosterone may cause virilization, and for this reason some authors prefer oestrone. Inunction of external genitalia with oestrone or testosterone cream has been advocated. True frigidity of long standing—that is, inability to experience or elaborate psychically sexual stimuli—is a rare condition, and probably cannot be improved by hormones.

Homosexuality and Excessive Sexuality.—The direction of homosexual or heterosexual drives cannot be altered with sex hormones; but the force of sexual drive in males can be reduced by treatment with female sex hormones. There are a number of papers on the subject, and all the authors are in general agreement about the indications and the rationale. Treatment with female sex hormones reduces the production of gonadotrophic hormones, producing a secondary effect on testicular function and secretion. The reduction of sex drive is comparable to that achieved by surgical castration, although some authors claim that endocrine treatment is more effective (Hamilton, 1943). Stilboestrol is the usual preparation, administered in increasing doses until the nipples become pigmented and the breasts sore; an alternative is ethynol oestradiol, 0.5 or 1 mg. daily. Eventually almost complete testicular atrophy will be produced, but not necessarily a total suppression of the abnormal sex drives. It is interesting that notice has been taken of this treatment at the recent trial of an extreme and persistent homosexual offender, in whom abnormal behaviour had continued in spite of the production of almost complete atrophy of the testes by stilboestrol. The judge took into consideration that the offender had therefore done everything possible that medical treatment could offer, although in his case it had not been completely successful. Persistent homosexual offenders should therefore be encouraged to persevere with this treatment, although in some cases a satisfactory control of sexual behaviour may not necessarily be achieved.

Male Climacteric

The gradual diminution in the production of male sex hormones in middle and later age is held to be responsible for loss of physical and mental powers and libido. The male climacteric as an entity has been well discussed by Spence (1954). The diagnosis of male climacteric reaction cannot often be made with confidence, because arteriosclerosis or other systemic diseases complicate the picture and there is no dramatic event like the cessation of menses to indicate endocrine change. Moodiness, irritability, tearfulness, inability to concentrate, paraesthesiae, and sometimes hot flushes, suggest the diagnosis. Treatment is with testosterone by injection, 25 mg. daily or thrice weekly until there is improvement, methyltestosterone 5 to 10 mg. three times a day being given as continuation therapy for a year or more. There is usually improvement in mental and physical activity, sexual performance, and altered sense of well-being. Better peripheral circulation and flushing of the face are favourable early signs.

Cretinism

A causal association between thyroid deficiency and failure of intellectual and physical development, known as cretinism, was observed early in the history of modern medicine. Some authors make a distinction between juvenile myxoedema and cretinism. The cretin suffers from athyreosis from intrauterine life or early infancy (Means, 1948). The clinical picture is well known, but the results of treatment are less certain, for good results cannot be obtained in infantile myxoedema unless the brain is free from congenital abnormality.

At one time it was believed that only early and cautious treatment was likely to be successful. Surveys by Lewis *et al.* (1937), and by Topper (1951), who gives a good bibliography, indicated that promptness and continuity of thyroid treatment did not altogether decide whether a child remained backward or not. Topper pointed out that, according to electroencephalographic studies, cerebral defect explains much of the mental deficiency of the treated cretin, and that when such a defect is present in infancy no amount of thyroid can improve the brain. In her large series, 39% remained defective in spite of treatment.

Treatment should be pushed to the point of tolerance, which can be found by trial and error. The small doses usually recommended in cretinism are based on requirements necessary for alteration of hair and skin, and do not produce acceleration of growth and intellectual development. While tolerance is being determined the patient should be kept in hospital. Means and Lerman (1935) pointed out that with a constant daily dose the maximum

effect is not produced for about three weeks, and it is not safe to increase the dose oftener than every three to four weeks. Toxic symptoms are rapid pulse, a small rise in temperature initial loss of weight, increased nervousness, and frequent bowel movements; and some authors believe that these occur at the limit of safety and can be tolerated for a while. Dangerous symptoms due to excessive dosage are extreme restlessness, twitching, diarrhoea, vomiting, continued loss of weight, very rapid pulse, high fever, and syncope. As much as 4 gr. (260 mg.) daily is given at 21 months without adverse effect, but average doses are: 6 to 18 months, ¼ to 2½ gr. (30 to 160 mg.); 1½ to 8 years, 1 to 2 gr. (65 to 130 mg.); 8 to adolescence, 1½ to 3 gr. (100 to 200 mg.). It is worth noting that the dose tolerated is not proportionate to the age and weight, for a young cretin can tolerate as much as a 12-year-old child with hypothyroidism (Brown, 1951).

Psychiatric Disturbances in Endocrine Disorders

Although psychological disturbances are a feature of many endocrine disorders they rarely amount to recognized psychiatric syndromes. Classical psychoses are uncommon even in thyrotoxicosis. Treatment of some endocrine conditions may precipitate a psychotic episode.

Thyrotoxicosis often follows an acute emotional upset, and it has been contended that it occurs usually in frustrated and emotionally dependent individuals who wish to take care of others. Ham *et al.* (1951) have agreed with some others that symptoms of thyrotoxicosis can be understood as the patient's response to early experiences and that although the experiences differ in detail they fall into a pattern characteristic of the disease. In all the patients they studied there were extreme feelings of insecurity in early life, a strong sense of responsibility, but a tendency to suffer in silence; this is in some contrast to the anxious patient, who has no such tendency. From the psychosomatic point of view, some cases of thyrotoxicosis may be an end-result of an endocrine disturbance operating through emotional pathways. Thyroidectomy may be followed by a degree of myxoedema, producing the usual sluggishness. Where there has been a coexisting anxiety state, or the diagnosis should have been an anxiety neurosis and not thyrotoxicosis, sometimes the thyroid requirements of body and brain are not met. The patient will be less able to cope with the anxiety situation than before operation, and the picture will then be continuing anxiety with agitation or even restless delirium. Treatment with thyroid hormone is indicated.

Myxoedema usually produces apathy and sluggishness. The administration of thyroid hormone may activate a paranoid psychosis, as if, by increasing metabolism, an uneasy psychological balance had been disturbed. Withdrawal of thyroid is not necessarily followed by an improvement in the psychiatric state, and cases of chronic paranoid psychosis arising in this way are occasionally seen. Caution is necessary in treating myxoedema in patients of paranoid constitution. Myxoedema may be associated with confusion and depression, especially in later life (Asher, 1949). A picture of organic brain change, with clouding of consciousness, delirium, or agitation, may be due to myxoedema or its cardiac complications (Calvert *et al.*, 1954). In such states of hyperactivity myxoedema may be overlooked unless remembered. Many of these patients improve with thyroid hormone; but care is neeeded, for an increased metabolism in the aged or in organic brain disorder may produce accentuation of confusion, delirium, and death.

Addison's Disease.—In adrenal hypofunction the capacity for adaptation is reduced. Cleghorn (1953) has compared the psychological changes in Addison's disease with myxoedema, and agrees with Engel and Margolin (1942) that the psychiatric symptoms of apathy, negativism, depression, and irritability occur in more than 50% of cases; he also quotes Stoll (1953), who reported similar disturbances in 35% in the pre-Addisonian state and 66% in the developed condition; according to Stoll, they all improved remarkably under treatment with cortisone.

Adrenogenital Syndrome.—Virilism in females due to adrenocortical hyperplasia or cortical tumours has been the subject of much study. Broster *et al.* (1938) and others have shown that in extreme cases a combination of aggressiveness and paranoid thinking are to be expected. It has been claimed that after operation a more normal adrenal function is accompanied by reduction in psychopathic elements. These are extreme conditions, and operation seems to be very seldom indicated. Nevertheless, this work suggests that further research in the relationship between hypercortical adrenalism and aggressive paranoid behaviour might be worth while.

Experimental Endocrine Treatment

Endocrine treatment in the psychoses is still in the experimental stage, since up to the present no conclusive evidence has been produced about its rationale and value. In spite of the views expressed by some workers there is nothing to suggest that a new system of psychiatric diagnosis or classification can be derived from endocrine investigations, and classical concepts cannot be disregarded, nor can laboratory methods replace clinical observation.

Most analytic methods so far evolved lack precision, and it is not certain what are the range and the significance of normal values in non-psychotic individuals, how much variation within the range normally occurs, and how the values are affected by age, sex, physical illness, diet, and state of nutrition.

Therapy directed on the basis of figures alone is notoriously unsatisfactory in general medicine, and is even more open to error in psychiatry. In a series of 150 recent and chronic psychotics, with some psychoneurotics, treated on laboratory indications at the Bristol Mental Hospitals, only 12 showed a significant improvement considered to be due to the hormone therapy. Psychiatric recovery or deterioration does not necessarily correspond with laboratory findings.

Nevertheless, in spite of the limitations of the methods, and the impossibility of defining scientifically the dimensions of psychiatric illnesses and degrees of improvement or deterioration, there is a good deal of evidence to justify research in the field of experimental endocrinology, with a hope of eventual therapy in some conditions.

Gjessing (1938) has shown that in the rare condition called periodic catatonia, alterations in nitrogen balance coincided with the catatonic episodes, and the attacks could be terminated or aborted by treatment with thyroxine and dried thyroid to discharge nitrogen stored. The value of Gjessing's treatment has been confirmed by other workers.

Many psychotics, especially schizophrenics, do not react normally to hormones. It has been shown that schizophrenics are, or soon become, insensitive to thyroid; and insulin resistance in schizophrenia is well known. The same seems to be true for cortisone and A.C.T.H.: neither depressives nor schizophrenics usually exhibit the euphoria and emotional changes described in normals. Hench *et al.* (1950) and others believed that the familiar euphoria was not due to relief of pain, but a positive factor accompanied by increased mental function. Some workers have assumed that psychological changes were most marked where there was some evidence of previous mental illness or psychological maladjustment; this is certainly not the case. Lewis and Fleminger (1954) have shown that of 12 patients with a history of recent mental illness who had been treated with cortisone or A.C.T.H. none developed a severe mental illness. In the Bristol Mental Hospitals, A.C.T.H. has been used extensively, and reactions comparable to those described in normals have never been seen. This suggests that in some psychiatric disorders the ductless gland system is abnormal; it may be insensitive or react in an abnormal way, or metabolic processes may destroy or neutralize the action of hormones.

A great amount of research in the endocrinology of schizophrenia, especially of the adrenal cortex, has been carried out at various centres. Evidence of failure to preserve adequate endocrine equilibrium and of abnormal adrenal responsivity has been advanced, but the treatment of schizophrenia with A.C.T.H. on the assumption of evidence of lack of adrenal stimulation, attempted by Glaser and Hoch (1951), by the Worcester group (Hope *et al.*, 1952), by Kobbernagel *et al.* (1953) in Scandinavia, and at the Bristol Mental Hospitals and elsewhere, has been practically unsuccessful.

Cortisone has been used, on the whole without much success, but Cohn *et al.* (1953) have reported that 6 out of 21 chronic patients who had been ill for about six years were discharged from hospital. Their patients were treated with between 300 and 800 mg. daily for four weeks. Toxic effects were observed in four at least, with oedema, retention of urine, and renal colic. It is possible that those who improved did so because of the destructive action of cortisone on the hypothalamus.

Castor *et al.* (1951) have shown that A.C.T.H. in rats produced degeneration of the paraventricular nuclei of the thalamus; cortisone did the same, but it also produced changes in the thalamic and hypothalamic nerve cells. These areas are usually affected by prefrontal leucotomy, and it is probable that Cohn's success was due not to the physiological but to the destructive effect of the cortisone.

Treatment with thyroid has been recommended in various conditions. Danziger and Kindwall (1953) have reported success in a number of cases of schizophrenia in which failure to remain in remission after other forms of treatment, or periodic fluctuations, seem to be common features. Their material may include cases of Gjessing's type. It is therefore worth while administering thyroid to the point of toxicity empirically in relapsing schizophrenia after E.C.T. and insulin-coma therapy have been unsuccessful. Thyroid is valuable in reducing apathy in schizophrenics after insulin coma (Mayer-Gross *et al.*, 1954).

Yet the role of the thyroid in psychiatric illness is still quite uncertain. Reiss (1954), using a radioactive technique, has reported that the thyroid activity was within the limits he regarded as normal in about 70% of psychiatric admissions. In a selected series of 450 cases, after treatment by various methods, including hormones, E.C.T. and insulin coma, the thyroid activity was reported as "normal" in 72%. This suggests that the thyroid state is of consequence in only a very small percentage of psychiatric cases, if at all, irrespective of whether the thyroid activity is regarded as causally related to the illness or indirectly as an indicator of the state of the endocrine equilibrium.

In manic-depressive psychosis A.C.T.H. has been used as an alternative to E.C.T., on the assumption that E.C.T. exercises its favourable effect by the mobilization of anterior pituitary hormones. But, although in a very few cases remissions have been seen after a single dose of 25 mg. of A.C.T.H., this hormone is practically valueless in depression and without effect in mania, as Cleghorn *et al.* (1950) and the Worcester group have reported.

Sands (1954) recommends dehydro*iso*androsterone ("diandrone") for young inadequate psychopaths with timidity, physical immaturity, little energy, and perhaps homosexuality; to combat the residual disabilities after insulin coma therapy in schizophrenia; in stammering, on a basis of inadequacy; and to assist psychotherapy in some cases of neurosis. Strauss *et al.* (1952) originally gave three criteria: abnormal 17-ketosteroid excretion, a mild or slowly deteriorating mental illness, and the appearance of physical immaturity. They regarded the normal ketosteroids as 6 to 21 mg. per 24 hours, and the beta fraction 5 to 15%. Diandrone is contraindicated where there is evidence of aggressive traits. Dosage is 5 to 30 mg. orally. Overdosage is suggested by undue irritability and overactivity.

Summary

There is a place for endocrine treatment in psychiatry, and the psychiatrist is often confronted with complications of the menses, the menopause, disturbance of libido, homosexuality, male climacteric, and cretinism. Treatments for these are reviewed.

In the field of the psychoses there is some evidence of endocrine disturbances, the exact nature of which is not yet clear. Random cures of psychotic conditions are always to be expected, but they contribute little to the understanding of the physiology of mental disorders.

Assuming that functional derangements of endocrine balance occur spontaneously and are responsible for psychotic illnesses, spontaneous remissions are to be expected, which must make one extremely cautious in attributing recovery to a particular therapy. It is probable that there is a time lag between alteration in physiological state and the appearance of mental change, which would make a reliable correlation of physiological and clinical observations difficult.

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"For doctors in Nyasaland the mango season means a plague of 'mango fractures.' Every year about this time the hospitals, especially in Zomba, the capital, are crowded with piccaninnies with broken limbs, plaster-of-paris hallmarks of an over-ambitious pursuit of the delectable fruit. Recently in Zomba there were eight small African boys with fractured legs—all victims of the mango craze, and all very sorry for themselves. But the little devils will never learn so long as their elders fail to set a good example of careful climbing and cautious picking: in a village not far from Zomba two Africans, grandfathers both, broke their arms when falling from mango trees, which often reach a height of sixty and seventy feet. Mangoes, incidentally, which were probably introduced into the Protectorate by Arab slave traders, are the most widely cultivated tropical fruit. They say Buddha often rested in the shade of mango trees. He would be unwise to take the risk in Nyasaland."—*Manchester Guardian.*

SPONTANEOUS AND INDUCED WATER INTOXICATION IN TWO CASES OF HYPOPITUITARISM

BY

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It has been known for many years that patients with adrenocortical failure, whether this be primary or secondary to anterior hypopituitarism, are unable to excrete ingested water at the normal rate (Rowntree and Snell, 1931; Robinson *et al.*, 1941; Levy *et al.*, 1946). Less recognized is the possibility that patients with hypopituitarism may retain water in excess of electrolytes while on ordinary diets and without apparent forcing of their fluid intake. Such water retention* would lead to dilution of body fluids (hypotonicity) and, finally, to symptoms of water intoxication. Whittaker and Whitehead (1954) have described the case of a patient with hypopituitarism whose death they attributed to spontaneous water intoxication. The present report describes two such cases in which a similar, though reversible, abnormality was observed.

Apart from its spontaneous occurrence, water intoxication is occasionally precipitated by water-diuresis tests in patients with hypopituitarism. Pickford and Watt (1950) have reported this complication, which also occurred in both of our patients.

In primary water retention the plasma sodium concentration falls, although the total body sodium may not be reduced. The plasma sodium concentration may also be low in severe sodium depletion, a finding which, by itself, is often regarded as evidence of depletion of this ion. It is important, therefore, to distinguish between these two hyponatraemic states, since they differ in cause, metabolic effects, and treatment (Wynn and Rob, 1954).

Briefly, sodium depletion leads to loss of body water and haemoconcentration. The patient loses weight, looks haggard, and shows loss of tissue turgor. The circulation is impaired, the blood urea rises, the plasma potassium may be raised, and there is usually a metabolic acidosis. If the kidneys behave normally there is little fall in plasma sodium concentration until loss of this ion is more than 300–500 mEq (McCance, 1936), because water is at first excreted to maintain a normal osmotic pressure of the body fluids.

With primary water retention there is no dehydration but the reverse. The body weight exceeds normal, and the circulation does not fail unless hypotonicity is extreme. The plasma sodium concentration is always low; acidosis and urea retention may be absent, and the plasma potassium concentration may be normal or low. The symptoms of water intoxication are not unlike those of sodium depletion, but with certain differences (Wynn and Rob, 1954). Gross hypotonicity causes weakness or great prostration, lethargy, anorexia, vomiting, mental disturbances, and, finally, convulsions and coma, which may prove fatal.

The following two cases of hypopituitarism illustrate the occurrence of water intoxication, both spontaneously and after a water-excretion test.

Case 1

M. W., a woman aged 53, had suffered from anterior hypopituitarism since 1941, when her pituitary gland was removed for mild acromegaly. In May, 1953, she came into St. Mary's Hospital for investigation, having had no specific treatment for her condition. She had had amenorrhoea since the operation and had long complained of weakness, tiredness, and difficulty in keeping warm; her incapacity was such that she had hardly left her bed for many years. On examination there were slight skeletal signs of acromegaly. She was thin, pale, and expressionless. Her speech was slow, monotonous, and slurred. There was loss of eyebrows and of axillary and pubic hair. The thyroid gland was not palpable. There were no abnormal cardiovascular, urinary, or neurological findings, and the blood pressure was 130/70. There were no signs of dehydration, and her weight was 52.3 kg.

The following investigations were made: urinalysis negative; Hb, 12.6 g.%; plasma sodium 116, potassium 4.1, chloride 83, and total CO_2 26.2 mEq per litre; plasma non-protein nitrogen, 20 mg. per 100 ml. (Table I).

TABLE I.—*Case 1: Blood and Plasma Chemistry, Blood Pressure, and Weight*

Day	Hb. (g.%)	Haematocrit	Na (mEq/l.)	K (mEq/l.)	Cl (mEq/l.)	Total CO_2 (mEq/l.)	N.P.N. (mg./100 ml.)	Protein (g./100 ml.)	B.P. (mm. Hg)	Weight kg.	Weight lb.
−14*	12·6	—	116	4·1	83·0	26·2	20	—	130/70	52·3	115·2
1	10·5	—	125	4·2	88·5	28·0	20	6·2	130/70	52·3	115·2
2	10·6	35·5	125	4·1	88·0	27·2	20	6·5	140/85	52·3	115·2
3	11·4	36·5	132	4·7	95·0	26·4	21	7·1	135/80	50·2	110·5
5	11·5	36·5	136	4·3	97·0	27·8	22	7·3	138/85	50·2	110·5
9	11·2	35·5	136	3·7	98·0	28·1	26	6·5	130/75	50·6	111·3
21	12·4	40·5	122	3·6	85·0	25·7	20	7·2	116/75	50·8	111·8
22	12·8	40·0	130	3·7	93·5	25·1	24	8·0	117/77	49·2	108·3
23	12·2	39·5	136	3·9	96·0	27·6	24	7·3	118/70	49·1	108·0

* Day −14 was soon after admission to hospital. The metabolic balance study began 2 weeks later (Day 1). Cortisone (100 mg. daily) was given on day 2 to day 9, and again on day 21 and subsequently.

TABLE II.—*Endocrine Function in Cases 1 and 2*

Tests of Endocrine Function	Case 1	Case 2
Gonadotrophic: Urinary F.S.H. excretion (m.u./24 hrs.)	—	<4
Adrenal cortex: Urinary 17-ketosteroids (mg./24 hrs.)	1·5 1·3	0·7 1·2
Urinary 17-hydroxycorticoids	Trace only*	Trace only†
Plasma 17-hydroxycorticoids‡ (μg./100 ml.)	1	0
Water diuresis: % dose excreted in 3 hrs.: (a) without cortisone (normal = 70% excretion of 20 ml. water/kg. in 3 hrs.)	9·5	6; 8·5; 12
(b) with cortisone	69	80; 66
Fasting blood sugar (mg./100 ml.)	89	60; 61; 64
Insulin tolerance (0·1 unit/kg.)	Hypoglycaemic—unresponsive	Hypoglycaemic—unresponsive
E.C.G. voltage	Low	Low
Thyroid: B.M.R. (% normal)	—	−48
I^{131} neck uptake at 48 hrs. (% dose) (lower limit of normal = 25%)	0	5·1
Urinary excretion 0–48 hrs. (% dose) (normal range = 35–70%)	82·7	73·3
"T" factor (normal range = 3–14)	1·8	1·4
Plasma cholesterol (mg./100 ml.)	207	389

* By courtesy of Dr. C. H. Gray.
† By courtesy of Dr. C. L. Cope.
‡ By courtesy of Dr. R. I. S. Bayliss.

*Unfortunately the term "water retention" is used in two senses in clinical medicine. Most commonly it is used to imply isotonic retention of both water and sodium, a condition which finally results in pitting oedema. The second sense, used in this report, means that water is retained alone or in excess of electrolytes. Since about two-thirds of this water is located in the cells (Wynn and Rob, 1954) the result is not pitting (extracellular) oedema but intracellular overhydration and dilution of body fluids.

Tests of endocrine function, showing adrenal and thyroid failure, are summarized in Table II. A water diuresis test of adrenal function, performed in ignorance of the low plasma sodium concentration, caused severe symptoms of water intoxication, including great prostration, nausea, vomiting, mental confusion, and a fall of blood pressure to 80/50. Only 9.5% of the litre of water given was excreted in three hours.

Experimental Observations

Methods.—Fourteen days after the episode of water intoxication described above a metabolic balance study was carried out. The patient was put on a diet containing about 50 mEq of sodium a day. Duplicate diets were bulked for three days and analysed for sodium, potassium, chloride, and nitrogen. Aliquots of three-day stool and 24-hour urine

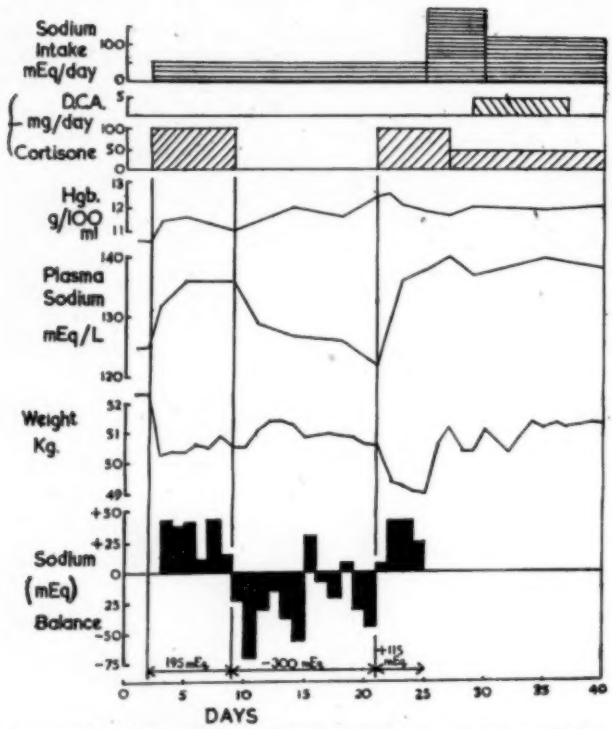

FIG. 1.—Metabolic balance data in relation to cortisone therapy in Case 1.

collections were also analysed. The patient was weighed daily before breakfast, after emptying the bladder, and when possible after defaecation, on scales sensitive to 30 g. (1 oz). After 24 hours on this diet, body weight and plasma electrolyte concentrations having stayed constant, she was given 100 mg. of cortisone a day by mouth, in four divided doses, for one week; cortisone was then discontinued. After a 12-day interval with no treatment the cortisone therapy was repeated.

Results (Fig. 1, Table I).—Twenty-four hours after starting cortisone the following changes were observed. The body weight had fallen by 2.05 kg. (4.5 lb.) owing to a large water diuresis (4,200 ml. of urine in 24 hours, which contained a total of 48 mEq of sodium and 74 mEq of potassium). The balance of water and electrolytes was: water −2 litres; sodium ±0; potassium −30 mEq. The plasma sodium had risen from 125 to 132, and chloride from 88 to 95 mEq per litre.†

During the next 48 hours there was no further change in body weight, and the plasma sodium rose to 136 mEq per litre. At this point—that is, 72 hours after starting cortisone—the cumulative balances were: water −2 litres; sodium +80 mEq; potassium ±0. The serum protein and Hb concentrations had risen slightly, suggesting haemoconcentration. The patient felt very much better whilst on cortisone; there was an increase in muscle power and animation, and her facial colour improved.

During the seven-day period of cortisone treatment 195 mEq of sodium was retained and 38 mEq of potassium lost, and during the latter half of this period the gain in weight was 0.4 kg. (0.9 lb.).

On stopping cortisone for 12 days the plasma sodium fell from 136 to 122 mEq per litre. There was a negative sodium balance of 300 mEq. However, instead of the expected fall in body weight, there was a small rise (0.2 kg., Table I). Thus, the usual renal regulation of osmotic pressure did not occur and water was retained in excess of electrolytes, resulting in severe hypotonicity. The patient's previous symptoms of weakness and lethargy returned.

On repeating the cortisone treatment (100 mg. a day) there was a prompt water diuresis, loss of weight (1.7 kg.), and a rise in plasma sodium concentration from 122 to 136 mEq per litre during the first two days (Fig. 1), during which time only 55 mEq of sodium and 45 mEq of potassium were retained. Clinical improvement was immediate.

These data suggest that the low plasma sodium concentrations present on each occasion before cortisone treatment were due mainly to spontaneous water retention. They also

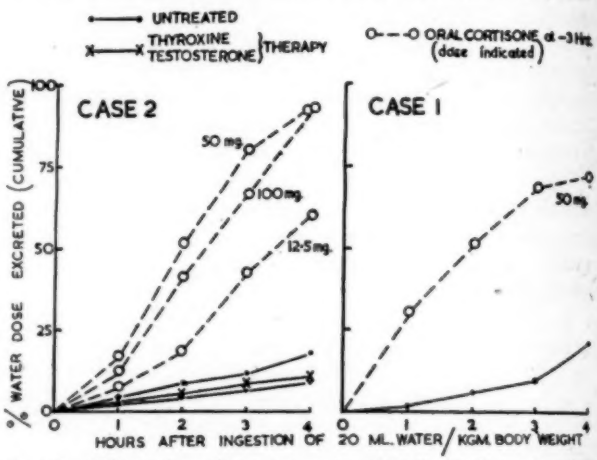

FIG. 2.—Effect of cortisone on water diuresis in Cases 1 and 2.

show that cortisone acutely corrected the sodium dilution. Further tests showed that cortisone acutely restored the ability to excrete a water load rapidly (Fig. 2). Since clinical improvement followed restoration of a normal plasma sodium concentration, it is possible that the symptoms were attributable, partly at any rate, to hypotonicity.

During six weeks of treatment with cortisone (50 mg. a day), later supplemented by D.C.A. (2.5 mg. a day), and a sodium intake of 125–200 mEq a day, the highest weight recorded was 51.5 kg. (113.3 lb.). This was less than the patient's initial weight (52.3 kg.), which further supports the interpretation that there was originally excessive water retention.

Case 2‡

J. B., a housewife aged 53, was admitted to Hammersmith Hospital in January, 1953, with an initial diagnosis of myxoedema. However, at 40 she had had a severe postpartum haemorrhage which had needed blood transfusion and which was followed by complete failure of lactation. The menopause at 51 was followed by the onset of myxoedema, which had become gross by the time of her admission.

†On simple osmotic theory, the expected and the observed rises in plasma sodium were close. Thus, assuming the total body water initially to be 65% of body weight—that is, 34 litres—then the final sodium should have been approximately $\frac{34 \times 125}{32} =$ 133 mEq per litre.

‡This case has already been described briefly in relation to her episodes of hypopituitary coma (Caughey and Garrod, 1954).

Her behaviour, voice, and appearance were those of classical myxoedema, with superadded features of hypopituitarism. In addition to loss of eyebrows and partial baldness of the scalp, there was total loss of axillary and pubic hair and absence of cutaneous pigment. There were no abnormal findings in the cardiovascular, urinary, or neurological systems, and the blood pressure was 140/90.

The following investigations were made: urinalysis, negative; Hb, 11.4 g.%. Tests of endocrine function showing gonadotrophic, adrenal, and thyroid failure are summarized in Table II.

Clinical Observations

The patient gained 3 kg. (6.6 lb.) in weight during her first three days in hospital. Two days later she became nauseated and stuporous after a water diuresis test, and the blood pressure fell to 100/70. She had excreted only 9% of the water dose of 1,320 ml. during four hours, and had remained oliguric during the next 24 hours. The plasma sodium was 116 and the chloride 85 mEq per litre, and blood urea was 21 mg. per 100 ml. She was then given 100 mg. of cortisone by mouth, 5 mg. of D.C.A. by intramuscular injection, and an infusion of 600 ml. of 5% glucose in 0.3% saline. Within 24 hours of starting treatment she passed large volumes of urine, lost 1.9 kg. (4.2 lb.) in weight, and regained full consciousness. Later she was discharged on thyroxine and a testosterone implant.

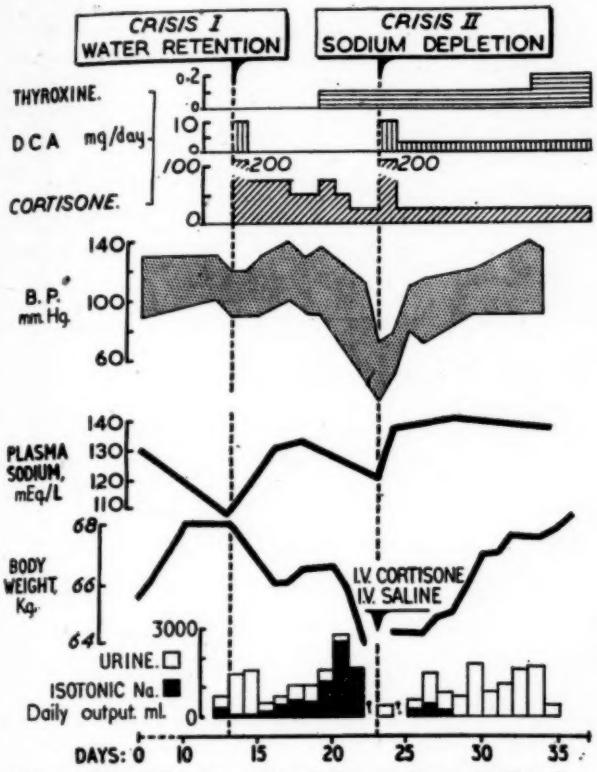

FIG. 3.—Metabolic changes in relation to therapy in Case 2.

In November, 1953, she was readmitted in relapse, having omitted to take any treatment for five months. The blood urea was 16 mg. per 100 ml., plasma cholesterol 389 mg. per 100 ml., and B.M.R. −36% (Robertson and Read). Her subsequent course is charted in Fig. 3. By the 13th day in hospital, while on a normal diet and without specific treatment, she had gained 2.5 kg. (5.5 lb.) in weight. The plasma sodium had fallen from 130 to the very low level of 107 mEq per litre, and potassium from 5.7 to 4.2 mEq per litre. On the 12th day she was nauseated, and during the 13th day she became irritable, then drowsy and stuporous, with a blood pressure of 120/90. She was given 200 mg. of cortisone by mouth in divided doses and one 10-mg. injection of D.C.A., followed by 75 mg. of cortisone a day for three days. During the first two days on cortisone she passed 3.1 litres of urine containing only a trace of sodium, and by the third day she had lost 2 kg. (4.4 lb.) in weight and the plasma sodium had risen to 130 mEq per litre. Full consciousness returned within 24 hours of starting treatment with cortisone. The loss of weight, due to excretion of water without sodium, accompanied by a rise in plasma sodium of 23 mEq, suggests that the hypotonicity was due mainly to water retention.

While still on cortisone, an episode of true sodium depletion occurred, the signs of which differed from those just described. Seven days after starting cortisone therapy the patient became aggressive and mentally confused and began to pass large amounts of sodium in her urine (784 mEq in three days). The body weight fell by a further 2.5 kg. (5.5 lb.) in two days. The exact negative sodium balance was not known, but probably exceeded 500 mEq. On the 10th day of cortisone therapy she needed forcible restraint, and four hours after an injection of paraldehyde (10 ml.) became comatose and pulseless. Her appearance was that of severe dehydration. The systolic blood pressure fell to less than 70 mm. Hg, and at one time could not be measured. The plasma sodium had fallen only to 117 mEq per litre, as compared with 107 mEq during the previous episode of water retention when the circulation was relatively normal. This classic crisis of sodium depletion and dehydration was successfully treated with saline infusion, D.C.A., and intravenous cortisone.

Subsequently, tests showed that normal water diuresis could be restored within three hours by intravenous or oral cortisone, but not by prolonged treatment with testosterone (300-mg. implant) and thyroxine (0.3 mg. a day) (Fig. 2).

Discussion

Both of these patients retained water in excess of electrolytes while on ordinary ward diets. This was shown by a large gain in weight accompanied by a profound fall in plasma sodium concentration—to 116 mEq per litre in Case 1, and to 107 mEq per litre in Case 2. In both patients the water retention was corrected by cortisone, which caused a large water diuresis. The plasma sodium concentration rose towards normal, although there was little change in total body sodium. The stupor which accompanied the hypotonicity in Case 2, and the symptoms of weakness and prostration in Case 1, were relieved when the excess of water was excreted.

Following a water-excretion test, and superimposed on the chronic water retention, there were acute symptoms of water intoxication, including nausea, vomiting, severe prostration, mental confusion, and, in Case 1, a sharp fall of blood pressure. These untoward effects probably occurred because hypotonicity was already significant in both patients when the test was carried out. This interpretation is supported by the fact that later, when the plasma sodium concentration was normal, there were no symptoms from water-excretion tests, although retention of the water dose was roughly the same as before.

Despite much investigation, the cause of the failure of water diuresis in hypo-adrenal states is still uncertain (Lewis, 1953). Cortisone corrects this failure, whereas deoxycortone acetate, testosterone, and thyroid extract are largely ineffective (Slessor, 1951; Garrod and Burston, 1952). Since cortisone also prevents chronic over-retention of water in hypopituitarism, it is likely that the failure of water homoeostasis is mainly conditioned by inadequate adrenal secretion of 17-hydroxycorticosteroids.

In hypopituitarism it would appear that adrenocortical secretion of steroids may fail in a selective manner. Thus, androgen secretion, measured by 17-ketosteroid output (in the female), fails early; and 17-hydroxycorticosteroid secretion (cortisone and hydrocortisone), as measured in the blood (R. I. S. Bayliss and A. W. Steinbeck, 1954, personal communication) and urine (Cope *et al.*, 1951) is usually very low. Yet mineralo-corticoid secretion, now believed to be

aldosterone (Simpson *et al.*, 1953), which may not be dependent on pituitary control, seems to be adequate for the patient's normal needs; because severe sodium depletion, such as occurs regularly in untreated Addison's disease, is an unusual feature of adrenal failure secondary to hypopituitarism, unless it is provoked by infections, gastro-enteritis, or surgical stresses (Peters *et al.*, 1954; Caughey and Garrod, 1954). This conclusion is supported by the results of Luetscher and Axelrad (1954), who found normal amounts of aldosterone in the urine of two cases of severe hypopituitarism, although this steroid was absent in the urine of patients with primary adrenal insufficiency. It is not surprising, therefore, that pure water retention without significant sodium depletion can occur in hypopituitarism. That it may not be uncommon is suggested by reports of very low plasma sodium concentrations, without evidence of dehydration or crisis, in patients with this condition—for example Bartter *et al.* (1950), Waterhouse *et al.* (1952), Peters *et al.* (1954), and Aber *et al.* (1954)—a state of affairs which has usually been attributed to sodium depletion.

As though to protect themselves from water retention, and because of their lowered metabolism, which reduces the solute load to the kidneys, patients with advanced hypopituitarism usually drink very little, and their urinary volumes are correspondingly small (Case 1 was exceptional in that her urine output, when not on cortisone, was around 1.5 litres a day). Admission to hospital may present a definite hazard to such patients because of a tendency to force the fluid intake, especially when urine output is low. This should be avoided by special instructions to the nursing staff.

Daily weighing of the patient is the simplest way to detect large changes in water balance. A gain in weight accompanied by a fall in plasma sodium concentration suggests primary water retention. It should be stressed that dangerous hypotonicity can exist without clinical signs, and that peripheral oedema is not a manifestation of primary water retention (although the two conditions may occur together).

Once the danger of forcing fluids in hypopituitary patients is recognized, it follows that water-excretion tests are unwise when plasma sodium estimations show that significant hypotonicity already exists. If the plasma sodium exceeds 130 mEq per litre the diluting effect of a litre or so of water is unlikely to cause untoward symptoms. Since cortisone acts rapidly to cause water excretion in adrenal failure, it should be available for use whenever water-excretion tests are performed in these patients.

Conclusions and Summary

An abnormality of water balance is described in two patients with anterior hypopituitarism. Although their intake of fluids was not forced, they retained water in excess of electrolytes, causing dilution of the body fluids and symptoms of water intoxication. The diagnosis was suggested by a gain in weight and a very low plasma sodium concentration. When cortisone was given there was a prompt water diuresis and the plasma sodium concentration rose to normal, though there was little change in the total body sodium. Water retention may not be very rare in anterior hypopituitarism, although it appears to have been reported as such in only one other case (Whittaker and Whitehead, 1954).

In addition to chronic water retention, acute symptoms of water intoxication, including nausea, vomiting, extreme prostration, mental confusion, and stupor, were precipitated by water-excretion tests of adrenal function. This untoward effect of the test probably occurred because there was already excessive dilution of body fluids which was not recognized when the tests were performed. To avoid this complication, a water-excretion test should not be carried out until the plasma sodium concentration is known. If symptoms due to water retention occur in patients with hypo-adrenal function, cortisone should be given, whereupon the excess water will be excreted rapidly.

We wish to thank Professor G. W. Pickering and Dr. Russell Fraser for allowing us to study cases under their care.

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RESULTS OF PARTIAL GASTRECTOMY IN TREATMENT OF PEPTIC ULCER

BY

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Partial gastrectomy has now gained general acceptance as the operation of choice in the treatment of gastric ulcer, and although it is widely used in the treatment of duodenal ulcer its results therein are not so universally acclaimed. Because of its wide usage, much information has accumulated about the effects of the operation, particular attention being focused on the various disturbing after-effects produced.

This investigation was begun in an attempt to assess the value of the operation, and to determine whether partial gastrectomy was capable of relieving the patient of his ulcer symptoms, freeing him from irksome dietary rules, and restoring him to a satisfactory economic life.

Method of Follow-up

This survey is based on a personal follow-up of cases of peptic ulcer submitted to gastrectomy of the Polya type in one surgical unit in the years 1940 to 1951 inclusive. Of 481 patients surviving partial gastrectomy, both elective and emergency, 23 were found to have died of intercurrent disease. Of the remaining 458, 415 (90.6%) were traced and interviewed. Of these, 379 were interviewed personally by one of us with the aid of an agreed schedule of questions, and the results were graded jointly. Information regarding 36 patients who lived too far away to travel was obtained through the courtesy of their own practitioners. Because mild post-gastrectomy symptoms are common in the immediate post-operative period and usually improve or disappear

during the succeeding six months, no patient was interviewed until at least a year after operation.

An overall assessment of the success, or otherwise, of partial gastrectomy was made by classifying the results into three categories: "good," when a good or excellent result had been obtained; "satisfactory," when the patient was substantially improved in comparison with his pre-operative state; and "poor," when no marked improvement had occurred or the patient's condition was worse than before operation. Each patient was asked for an opinion regarding the success of the operation, and the observer made a separate estimate based on all aspects of the patient's health. No result was adjudged to be "poor" on account of anaemia alone, as this is in most cases correctable by the administration of iron. Seven patients who developed tuberculosis were regarded as "poor" results on the assumption of a close relationship between this disease and gastrectomy.

Clinical Assessment

The results are presented in Table I, and the number of patients satisfied with their post-operative state is seen to be very impressive. Only 16 patients out of 415 considered that they had obtained no benefit from partial gastrectomy. The stricter criteria of success adopted by the observers produce a different picture, and 50 (12%) were considered to have had a "poor" result from operation.

TABLE I.—*Clinical Assessment*

Result	Patient's Opinion	Observer's Assessment
Good	338 (81·4%)	266 (64·1%)
Satisfactory	61 (14·7%)	99 (23·9%)
Poor	16 (3·9%)	50 (12·0%)

On analysis there was found to be no significant correlation between the clinical result and such factors as the age of the patient, the duration of ulcer symptoms, and the site of ulcer; nor did variations in operative technique influence the outcome, as there was no significant difference in result between 276 antecolic and 131 retrocolic anastomoses.

In comparing the sexes (Table II) it was found that the number classified as "poor" was essentially the same, but fewer of the women were regarded as having a "good" result, a number of otherwise excellent results being classified as "satisfactory" owing to anaemia.

TABLE II.—*Result in Relation to Sex of Patient*

Sex	No. of Patients	Result as Assessed by Observer		
		Good	Satisfactory	Poor
Male ..	355	231 (65·1%)	81 (22·8%)	43 (12·1%)
Female ..	60	35 (58·3%)	18 (30·0%)	7 (11·7%)

Operative Mortality

With increasing experience of the operation and better pre- and post-operative management (Illingworth, 1953) it was found that the mortality rate of the operation gradually improved throughout the years of the series, and it is now 3.3% (214 cases, 1951–2).

Of all the factors investigated which might influence the mortality rate, the age of the patient was found to be the most important. Over 50 years of age the rate rose steeply and cardiac and respiratory causes of death contributed largely to the higher mortality in the older patients. The duration of ulcer history, the sex of the patient, and the type of operation performed did not affect the mortality rate to a marked extent.

Tuberculosis after Partial Gastrectomy

It is suspected that there is an increased liability to pulmonary tuberculosis after partial gastrectomy. Attention was focused on this possibility by Pulvertaft (1952), who found that of 23 deaths subsequent to operation 8 were due to tuberculosis. The occurrence of such deaths had previously been noted without comment by other authors (Bruusgaard, 1946; Ransom, 1947), but none found such a high incidence as did Pulvertaft.

In the present series there have been 8 deaths due to pulmonary tuberculosis in a total of 23 intercurrent deaths. In addition, 8 patients still alive were found to have had pulmonary tuberculosis, and in 6 of these the lesion was still active. Thus in 481 patients surviving operation, 16 (3.3%) are known to have developed active tuberculosis.

Such a figure would appear to be definite evidence of an increased liability to tuberculosis in patients who have undergone partial gastrectomy. It is therefore suggested that the presence of active tuberculosis in an ulcer patient should be accepted as an absolute contraindication to partial gastrectomy, and the presence of a latent lesion should give rise to serious consideration of the advisability of this operation. Since 1952 a pre-operative chest film has been taken routinely in this unit, and this would appear to be a wise precaution.

The reason for the increased liability to tuberculosis is not known, but Pulvertaft's suggestion that it is "related to the recognized loss of weight following gastrectomy" seems very reasonable. There is little doubt that the nutrition of many of these patients is inadequate, and this could be the determining factor in the development of tuberculosis.

Anaemia after Partial Gastrectomy

It is generally accepted that macrocytic anaemia with a megaloblastic bone marrow is very rare after partial gastrectomy, though more common after total gastrectomy. Only one case of atypical macrocytic anaemia occurred in this series, and we hesitate to label it as a verified case. Iron-deficiency anaemia, on the other hand, is far from uncommon and is generally thought to be due to the inadequate absorption of food iron after partial gastrectomy.

In this investigation the haemoglobin level, as measured by the Sahli method, was ascertained at each interview, and cases with values below 70% had a full haematological examination carried out. The results are plotted separately for males and females in Fig. 1. It will be seen that the haemoglobin level is subnormal in the majority of patients, especially females. The values for men tend to be situated in the range 80–95%, and for women 70–90%.

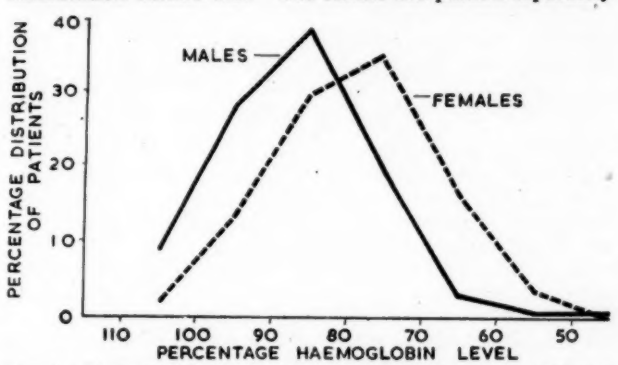

FIG. 1.—Haemoglobin levels. (Sahli: standard 14 g. per 100 ml.)

It is suggested that diminished iron absorption after partial gastrectomy produces, in general, a haemoglobin level lower than that of normal individuals. In some cases symptoms of tiredness or shortness of breath are produced, especially in women in whom the additional factor of menstruation is involved. The administration of iron by mouth is usually curative, and those who do not respond adequately can be controlled by periodic injections of intravenous iron.

Loss of Weight after Partial Gastrectomy

The occurrence of loss of weight after partial gastrectomy is accepted by most authorities (Everson, 1952; Pulvertaft, 1952), the degree of such loss depending on the standards adopted. In this survey, in each patient the post-operative

weight at the time of interview has been compared with his normal weight in health. The findings are presented in Table III and in Fig. 2, the change in weight being indicated according to the formula

$$\frac{\text{Present weight}}{\text{Normal pre-illness weight}} \times 100.$$

TABLE III.—*Change in Weight*

Change in Weight	Males	Females
+5% or more ..	27 (8·6%)	4 (7·8%)
−5% to +4% ..	114 (36·2%)	14 (27·5%)
−6% to −10% ..	81 (25·7%)	8 (15·7%)
−11% to −15% ..	56 (17·8%)	14 (27·5%)
−16% to −20% ..	30 (9·5%)	6 (11·8%)
−20% or more ..	7 (2·2%)	5 (9·8%)

The change in weight was calculated by expressing the present weight as a percentage of the normal pre-illness weight and thereafter noting the percentage gain or loss.

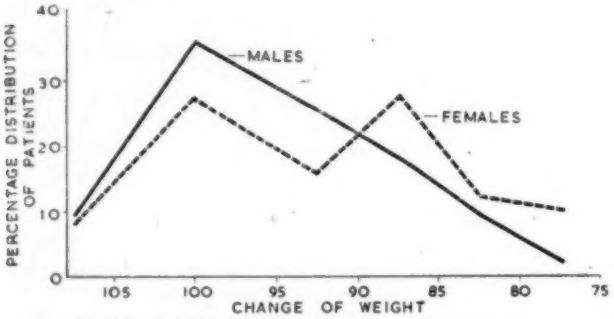

FIG. 2.—Weight change after partial gastrectomy

$$\frac{\text{Present weight}}{\text{Normal pre-illness weight}} \times 100$$

If it is accepted that a 5% loss of weight is within the limits of normality, 44.8% of males and 35.3% of females regained their pre-illness weight. This compares with Pulvertaft's figures of 53.9% for males and 37.2% for females. A substantial degree of weight loss (more than 10%) is noted in 29.5% of men and 49.1% of women. Such figures leave no doubt that loss of weight after partial gastrectomy is a real entity, and many patients are seriously disturbed by it.

Recurrent Ulceration

The frequency of recurrent ulceration after partial gastrectomy would appear to depend on the level of gastric resection (Visick, 1948). In this unit resection is performed above the lowest of the vasa brevia, and the gastric remnant is a tubular pouch about 2 in. (5 cm.) wide and 6 in. (15 cm.) long. With such a resection, acid secretion has been found to be negligible or absent, and, accordingly, the risk of recurrent ulcer is slight. In this series, recurrent ulcer was proved in only 4 out of 438 partial gastrectomies. Two of these were demonstrated by gastroscopy; one patient died from a gastro-jejuno-colic fistula and the fourth from recurrent haematemeses. Ulcer has been suspected on clinical grounds in another seven patients, but a full investigation, including laparotomy in two, has proved negative. In none of these patients has the pain responded to ulcer therapy, and it is thought that the symptoms are not due to ulcer.

This gives an ascertained recurrence rate of 0.9%. This accords with Visick's (1948) experience of measured radical gastrectomy (an even more extensive resection), when he noted no recurrence in 200 patients. If a less extensive resection is preferred in view of the probable lesser operative risk and the lower incidence of post-gastrectomy symptoms (Pulvertaft, 1952), a higher recurrent ulcer rate must be accepted—for example, 3.7% (Visick, 1948).

Post-Gastrectomy Symptoms

Estimates of the incidence of these symptoms vary enormously with different observers up to the high figure of 75% (Muir, 1949). Symptoms do occur in many patients soon after operation but tend to diminish or disappear within the first six months, and in some cases are acknowledged only after careful inquiry. As our patients were not interviewed until at least a year had elapsed since operation, it was thought that a reasonable estimate of the incidence of symptoms was possible.

The following classification into four categories was adopted: (*a*) no symptoms; (*b*) fullness only—that is, a sensation of epigastric fullness induced by meals of small quantity (two small courses or less) without other symptoms; (*c*) "dumping"—mild or severe; and (*d*) bilious vomiting—mild or severe. Frequent overlap was found between the latter two categories.

Our estimate of the frequency of these symptoms is presented in Table IV. Severe symptoms were found to occur in 48 (11.8%), and consisted of severe dumping or severe bilious vomiting or both. Milder symptoms were more common but on the whole relatively unimportant. From a study of the results of other authors (Butt *et al.*, 1948; Visick, 1948; Capper and Butler, 1951; Goligher and Riley, 1952) it would seem reasonable to assume that the incidence of severe symptoms is in the region of 5 to 10%. Unfortunately, it often proves difficult to relieve this minority of their symptoms, and, although a variety of medical and surgical remedies have been tried, the results on the whole are disappointing.

TABLE IV.—*Post-gastrectomy Symptoms in* 408 *Patients*

Symptoms	Males	Females	Total
Nil	184	26	210
Fullness only	57	10	67
*Dumping { Severe	17	4	21
*Dumping { Mild	40	6	46
*Bilious vomiting { Severe ..	26	4	30
*Bilious vomiting { Mild ..	32	9	41

* Overlap between these two categories was relatively common.

Hypoglycaemia and Vitamin Deficiencies

Hypoglycaemia is generally accepted as the cause of late symptoms two to three hours after a meal. Both the incidence and the resultant disability were found to be of minor importance in this series.

Vitamin-C deficiency was seen in one of our cases, and vitamin-B deficiency occurred in 17 patients, mainly in the form of cheilosis and glossitis. No gross deficiencies were noted such as were recorded by Wells and Welbourn (1951), and response to treatment was satisfactory.

Economic Results of Partial Gastrectomy

After discharge from hospital, usually 10 days after operation, patients are encouraged to return to their original work as soon as they are reasonably capable of so doing. Those performing heavy manual labour naturally tend to restart after a longer period and sometimes have to change to a lighter occupation. It is highly desirable that patients should resume work as soon as possible, both for economic and for psychological reasons.

From Table V it is seen that convalescence need not be unduly prolonged, as 84.3% were able to resume full work within six months. Only 3% of patients have failed to return to work at any time since operation, though a larger number (7.3%) were not working at the time of the survey for various reasons—for example, unemployment, intercurrent illness, etc.

TABLE V.—*Time of Return to Work after Operation:* 395 *Patients*

Time of Return after Operation	No. of Patients	
1 month	38 (9·6%)	
2 months	109 (27·6%)	62·5%
3 ,, ...	100 (25·3%)	
4–6 ,, ...	86 (21·8%)	
7–9 ,, ...	20 (5·1%)	
10–12 ,, ...	13 (3·3%)	
Over 12 months	17 (4·3%)	
No return to work	12 (3·0%)	

If partial gastrectomy is to be regarded as a satisfactory operation, patients must not only return to work within a reasonable period but be able to retain their jobs in competition with other workers. That they are eminently capable of remaining in employment is shown by Table VI, in which

TABLE VI.—*Loss of Working Time (Male Workers)*

Time Lost	Year Before Operation	Year Before Follow-up	
		All Workers	Heavy Workers
Nil	21·6%	79·9%	84·0%
1 month	16·6%	6·1%	6·4%
2 months	13·4%	4·3%	5·3%
3 „	15·3%	1·2%	—
4–5 „	21·3%	1·8%	1·1%
7–9 „	7·3%	2·4%	3·2%
10–11 „	4·5%	4·3%	—

the amount of work lost in the year prior to interview is recorded. Little or no work had been lost by 79.9%, and, indeed, many of these had never lost even a day since their return to work. In fairness, it must be admitted that some with post-gastrectomy symptoms were fortunate that they were able to take things easily after meals.

To illustrate the improvement in economic status after operation, a comparison is made of the loss of work before and after operation (Table VI). The comparison is impressive and indicates the economic value to the patient of a satisfactory partial gastrectomy. So satisfied with these results are the patients that the annoyance of mild symptoms is usually ignored.

The ability of heavy manual workers to perform their original job was next investigated. Various occupations were classed as "heavy" (involving heavy manual labour or requiring physical exertion beyond that of the average worker) or "light" (sedentary work or work requiring relatively little physical effort), and the class of work to which each patient returned was noted. As is seen in Table VII,

TABLE VII.—*Return to Work after Operation:* 134 *Heavy Workers:* 261 *Light Workers*

	Heavy Workers	Light Workers
Return to original or equivalent work	97 (72·4%)	220 (84·2%)
„ „ lighter work	30 (22·4%)	19 (7·3%)
Unemployed (labour market, other health reasons, etc.)	6 (4·5%)	14 (5·4%)
Unemployed (due to post-gastrectomy symptoms)	1 (0·7%)	8 (3·1%)

72.4% of heavy workers returned to their former occupation or to one involving equivalent or, in some cases, even heavier duties. Not only do the majority of heavy workers return to their former occupation, but they lose surprisingly little work after they have restarted (Table VI). From this evidence it is seen that the majority of heavy workers can be restored to a satisfactory economic life by partial gastrectomy.

Discussion

The satisfaction expressed by the large majority of patients with the results of partial gastrectomy underlines its value, and the low percentage of dissatisfied patients (3.9%) is reassuring. Unfortunately, those patients frequently do not respond to treatment, and this gives grounds for disquiet when considering the results as a whole. A large number (29.4%) are troubled by mild or severe post-gastrectomy symptoms, but they usually feel that these are tolerable by comparison with the disabling pain of ulcer.

The attraction which gastro-enterostomy still holds for the surgeon lies in the lower mortality of the operation and the rarity of symptoms of "dumping," bilious vomiting, loss of weight, and anaemia, but the price paid in recurrent ulceration is high. In spite of this, gastro-enterostomy still has a place in the treatment of duodenal ulcer. Because women are more liable to anaemia and weight loss after partial gastrectomy, and the severity, though not the incidence, of stomal ulcer symptoms after gastro-enterostomy is less in women than in men (Clark, 1951), it is possible that the latter operation is to be preferred in females. Furthermore, in both sexes over 50 years of age the risk of stomal ulcer after simple anastomosis is less than average (Clark, 1951), and, as the mortality of partial gastrectomy rises so definitely with age, the simpler operation would appear to be preferable in older people.

In the largest group of duodenal ulcer patients—namely, adult males between 20 and 50 years of age—the risk of recurrent ulceration is such that it is considered that an extensive partial gastrectomy is desirable. In view of the evidence presented in this investigation, the results to be expected are good.

Even in those who do well, however, it is felt that something is lacking. Nutrition is substandard. In the majority the intake of food is limited to a less than average size of meal, and in some there is deficient absorption of fats with the occurrence of borderline fat absorption or actual steatorrhoea. The extent of the deficiency in the individual patient is indicated by the degree of weight loss, which is substantial in nearly 50% of cases. The absorption defect is also evident in the case of iron and vitamin B. In most cases absorption of these is sufficient to meet normal requirements, but in some a clinical deficiency results.

From the evidence of deficient absorption of proteins and fat (Wollaeger *et al.*, 1946), the tendency to loss of weight, the frequent presence of a subnormal haemoglobin level (Fig. 1), and the relatively frequent occurrence of vitamin deficiencies, it seems to us that a state not of malnutrition but of subnormal or substandard nutrition exists in a considerable number of cases after partial gastrectomy. This seems likely to be the precipitating factor in the development of tuberculosis or the reactivation of a quiescent lesion.

Summary

An assessment of the value of partial gastrectomy in the treatment of peptic ulcer is presented, based on a personal follow-up of cases operated on between 1940 and 1951. Particular attention was paid to the effect of the operation on the patient's working capacity, and the incidence of pulmonary tuberculosis, recurrent ulceration, loss of weight, anaemia, and post-gastrectomy symptoms was investigated.

Our thanks are due to Professor C. F. W. Illingworth for giving us access to the records of all these cases in which partial gastrectomy was performed in his unit in the Western Infirmary, Glasgow, and also for his advice and encouragement throughout this investigation. We are grateful to Miss Murray, the secretary of the Peptic Ulcer Clinic, for valuable clerical assistance.

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The Second Panhellenic Congress of Hygiene was held in Athens from December 5 to 11, 1954, under the honorary chairmanship of the Minister of Social Welfare, Dr. CHRISTOS S. SOLOMONIDES. Among the 500 who attended were members of the Academy of Athens, the University of Athens, the Athens School of Hygiene, the Panhellenic Medical Association, and the Athens Medical Association, together with representatives of public health, social welfare, and engineering.

TREATMENT OF HAEMORRHAGE FROM PEPTIC ULCER BY CONTINUOUS INTRAGASTRIC MILK DRIP

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" Where is the man who can live without dining ? "
—EDWARD BULWER-LYTTON (*Owen Meredith*).

During the last century haemorrhage from peptic ulcer was treated by rest, starvation, and opium. The patient, anxious and weakened from blood loss, lay flat, enduring starvation and dehydration, ice being applied to his abdomen and parched lips. In a widespread belief that the giving of blood restarted haemorrhage, transfusion was withheld and enfeeblement prolonged.

Literature

Early in the present century, Lenhartz (1904) advised feeding with milk and raw eggs from the first day. However, many hospitals in this country continued to employ initial starvation until Meulengracht (1934) introduced a further plea for early generous feeding. "It seems doubtful," he wrote, "whether it be particularly expedient to pick out for weakening dietetic measures the very point of time when a patient has lost a considerable amount of blood and is rather poorly." The 'thirties saw other important therapeutic advances: Marriott and Kekwick (1935) demonstrated the importance of adequate transfusion; Finsterer (1933) made, and Gordon-Taylor (1935) successfully defended, the case for early operation in patients with established ulceration and severe haemorrhage, pointing to lower mortalities if the gastrectomy was performed in the first 48 hours. Those tempted to question whether this advice is applicable now the patient has adequate food and transfusion during the first two days should note that Tanner (1951) has proposed, and is at present employing, a return to the Finsterer regime. Recent authors, such as Ogilvie *et al.* (1952), have stressed the importance of medico-surgical team-work in the management of bleeding ulcers.

With what appeared to be steady therapeutic advances in the first half of this century one would have expected a comparable decline in mortality. However, there was a rise during the first quarter of the century. The factors which caused this and led to subsequent confusion were stated by Avery Jones (1947) in the Goulstonian Lectures. Those wishing to learn the pitfalls of drawing conclusions from published mortalities are referred to these lectures.

Briefly, from 1902 to 1907 published ulcer mortalities were 7% or under. Some of these low figures gave a false impression of the mortality in the country as a whole as they came from teaching hospitals having a smaller proportion of indigent and elderly patients. Some series excluded cases transferred to surgical wards or did not take into account the overall hospital results. Omissions of deaths from causes related to the management of the haemorrhage were also common. Nevertheless, making allowances for these factors, Avery Jones was able to show that there was still a lower mortality due to the greater prevalence of acute ulcers in young women at this time, whereas after 1920 there were many more chronic ulcers in males over 40.

Between 1920 and 1932 relatively high mortalities were published. In 1927 Bulmer reported a mortality of 10.7% and in 1932 one of 13.5%. More reports came in from municipal hospitals which had poorer and older patients, among whom there was a greater proportion of gastric ulcer and a greater expectation of death from peptic ulcer haemorrhage. Of Avery Jones's patients, 33% were over 60, whereas former voluntary hospital series might have had only 10% of patients above this age. Mass hospital surveys might show even higher figures, and Chiesman (1932) reported a mortality of 25%. Comparable figures did not come from other parts of the world, and in Denmark, Meulengracht (1939), using generous feeding, showed only 1% mortality. However, only 30% of these patients showed radiological confirmation of ulcer.

Between 1935 and 1953 the mortality fell once more, and Avery Jones's (1947) figure of 8% may now be taken as a standard. These years reflected the improvement following adequate transfusion (Marriott and Kekwick, 1935), generous feeding (Meulengracht, 1939), and planned surgery (Finsterer, 1936; Gordon-Taylor, 1937).

Treatment by Continuous Intragastric Milk Drip

Impressed by the ulcer patient's rapid recovery from pain on a continuous intragastric milk drip, we looked for further improvement in feeding methods for bleeding peptic ulcer by combining the continuous intragastric milk drip employed by Winkelstein (1933) with early generous feeding as recommended by Meulengracht, the former being given as soon as the patient had settled in hospital and had received his morphine, the latter as soon as he wanted it, usually the morning of the second day. It was argued that such a regime would give adequate fluid replacement, complete nourishment, relieve the patient's shock, and reassure him. Furthermore, the continuous buffering action of the milk would bring early relief from pain, set the stage for early healing, and prevent pepsin from dissolving blood clot in the vessel mouth and ulcer base. The high morale and freedom from exhaustion and prostration in these patients has encouraged us to continue with this regime, although there is statistically little difference in its results from the one, previously adopted, of one-hourly milk feeds on the first day followed by a liberal diet on the second. It should be pointed out that the earlier group were fed generously and must not be regarded as a control group treated by restricted feeding. Both groups of patients received adequate transfusion.

Technique

The apparatus was simple, consisting of a Ryle stomach tube, a glass connexion, two lengths of rubber tubing, a drip chamber from a transfusion set, and a flask to hold the milk (see Fig. 1). The siphoning bottles used by Woldman (1936) for the continuous aluminium hydroxide drip were not employed. The mechanism of the drip was explained to the patient in simple terms: "This neutralizes the acid in your stomach and allows healing to go on during the night." The Ryle tube was passed nasally to the second mark or until gastric juice was obtained, when it was withdrawn slightly and strapped to the side of the face. It was considered an advantage to have the tip of the tube high in the stomach in order to "bathe" the ulcer area, while avoiding direct trauma from the tube. The American authors used a Levin tube or a collapsible tube made of latex (Woldman, 1937). The Ryle tube did not block easily.

and when the drip stopped it could often be restarted by milking the tube. The tube would be changed at varying times determined by discomfort or blocking, usually 48 hours; sometimes it was used for as long as seven days without replacement.

Initially milk was contained in blood transfusion bottles, but later vacoliter flasks were used instead, these having to be changed less often. The smaller bottles were still employed during the hot summer months. Five or six pints (2.8 or 3.4 litres) of milk was run in during 24 hours. The patient received a generous bland diet at four-hourly intervals while the drip was still running, and thus the total intake was in the region of 3,700 calories. This high-calorie feeding would be difficult to procure without employing continuous intragastric milk throughout the night.

FIG. 1.—Simple gravity feed with vacoliter bottle and Ryle tube.

The milk was usually unadulterated; on rare occasions aluminium hydroxide gel was added if there was some persistent pain unrelieved by the milk drip. In the earlier cases with recurrent bleeding, viper venom was added to the drip, but as it did not appear to influence the tendency to recurrences this practice was later discontinued. We have no experience of the addition of thrombin. Winkelstein's (1933) method of adding sodium bicarbonate was rejected, as continuous buffering was considered to be more important than rapid neutralization, and it was thought wiser to avoid the danger of alkalosis. The milk drip was preferred to the aluminium hydroxide drip employed by Woldman (1936), as the value of early nourishment with generous supply of calories, protein, and electrolyte was felt to outweigh the dangers of promoting peristalsis.

Nature of Series

The patients comprising this series have all been admitted to one of two of a small group of regional hospitals as emergencies with haematemesis or melaena due to peptic ulceration. They constitute the entire admissions of such cases in the group during the period between the summer of 1950 and the winter of 1953–4. In assessing the mortality no exclusions have been made for related deaths or the late complications of surgery. The proportion of peptic ulcer patients among the overall cases of haematemesis of the group is shown in Table I. The sex incidence, ulcer site, and mortality are shown in Table II.

TABLE I.—*Total Emergency Cases of Haematemesis or Melaena During Same Period*

Peptic ulcer	153
Carcinoma of stomach	8
Cirrhosis of liver, Oesophageal varices	6
Telangiectasis	1
Haemophilia	1
Uraemia	1

As the majority of patients were treated by the continuous intragastric milk drip after the summer of 1951, and the accuracy of the diagnostic indexing could not be ensured before the summer of 1950, the control group is a much smaller one.

Table III shows the distribution of the age groups and compares the mortalities with those of Cullinan and Price (1932) and Avery Jones (1943).

TABLE II.—*Sex Incidence, Site, and Mortality*

	Conventional Therapy and Early Feeding				Milk Drip			
	M	F	Total	Deaths	M	F	Total	Deaths
Duodenal ulcer	17	7	24	1	51	15	66	5
Gastric ulcer	5	3	8	2	10	2	12	1
Gastric and duodenal ulcer	1		1					
Acute lesion	7	11	18	1*	12	6	18	1†
Stomal ulcer	2	—	2		2	1	3	—
Oesophageal ulcer					1	—	1	—
Total	32	21	53	4 (7·5%)	76	24	100	7 (7%)

* Acute gastric erosion. † Acute gastric ulceration.

TABLE III

Age	Cullinan and Price (1932) (Haematemesis Only). Restricted Fluid Intake. Occasional Small Transfusions		Avery Jones* (Haematemesis Only). Generous Feeding—Witts's Regime. Adequate Drip Transfusion		Present series, 1951–3 (Haematemesis and Melaena). Continuous Milk Drip. Generous Feeding. Adequate Drip Transfusion	
	No.	Deaths	No.	Deaths	No.	Deaths
10–19	1	0	0	0	2	0
20–29	12	0	4	1	10	0
30–39	15	3	13	0	16	0
40–49	29	6	28	0	25	0
50–59	37	6	40	2	20	1
60–69	11	4	31	6	19	4
70–79	0	0	7	1	8	2
80+	0	0	3	0	0	0
Total	105	19	126	10	100	7

* Avery Jones excluded melaena alone from his figures for better comparison with Cullinan and Price's series. Our numbers are not large enough to make this worth while. Of our patients 27% were over the age of 60 and 47% over the age of 50. There were no deaths below the age of 52 and only one below the age of 60.

Analysis of Deaths.—In Table IV summaries of the seven fatal cases in the 100 drip-treated patients are given. In two cases death was directly due to haemorrhage. In two it was due to conditions associated with the management of the haemorrhage, and in three to later complications of surgery.

TABLE IV.—*Analysis of Deaths*

Age and Sex	Type of Ulcer	Operation	Day of Opn.	Cause of Death	Day of Death	Comments
M 52	G.U.	None		Haemorrhage	3rd	Sudden collapse. Necropsy: ruptured aneurysm of splenic artery in base of ulcer
M 67	D.U.	"		"	2nd	Necropsy: chronic nephritis, prostatic hypertrophy, hypertensive heart disease, duodenal ulcer
F 62	Acute G.U.	"		Pulmonary oedema	1st	Necropsy: aortic stenosis, acute pulmonary oedema, acute gastric ulcer
M 71	D.U.	Gastrectomy. Further opn.	1st 4th	Haemorrhage	5th	Haemostasis not secured at first operation
M 70	D.U.	Gastrectomy	2nd	Duodenal fistula and peritonitis	24th	
M 63	D.U.	"	14th	"	23rd	
F 60	D.U.	"	6th	"	12th	

Duration of Bleeding.—Fig. 2 is an assessment of the presence of occult blood in the stools (estimated in the laboratory by the benzidine test and in the ward by Gregerson's modification of it). A larger proportion in the continuous milk-drip group than the control group stopped bleeding between the 5th and 10th day, whereas the peak in the conventionally treated group was between

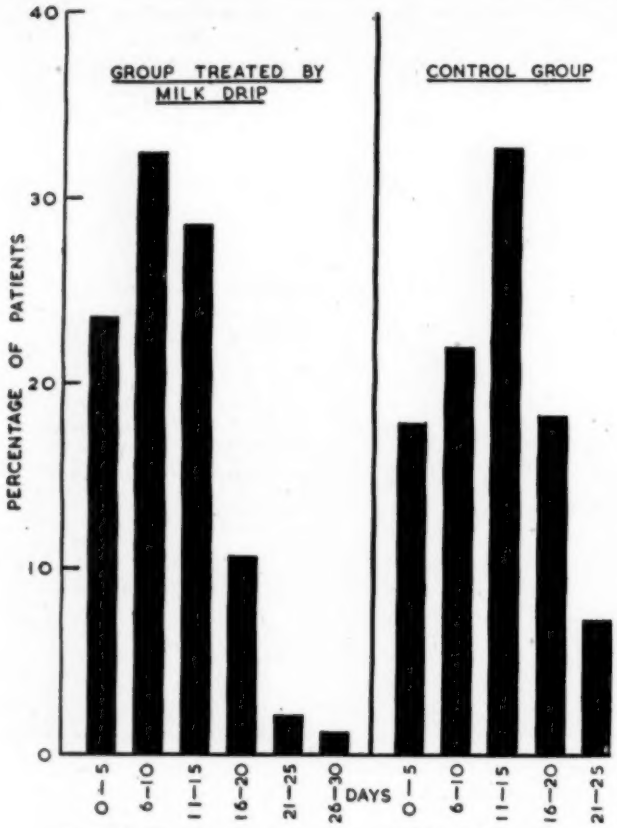

FIG. 2.—Showing duration of occult blood in stool.

the 10th and the 15th day. Turnbull and Sagi (1939) and Meulengracht (1934) have claimed earlier cessation of bleeding in groups of patients treated by initial feeding.

Recurrences.—At first sight the drip-treated group, though twice the size of the conventional one, gave rise to only six more recurrent bleedings. This figure is unconvincing when allowance is made for eight of the recurrences in the conventional group having occurred in one patient. If this patient is excluded one is unable to demonstrate a reduction in the number of recurrent bleeds in hospital as a result of drip treatment. Nevertheless it can be stated that to have more than two recurrences was exceptional in these 100 patients. The one with four recurrences had a deep penetrating posterior gastric ulcer, and his operation was deferred because of auricular fibrillation and congestive heart failure. Despite these handicaps he survived on medical treatment. The patient with eight recurrences in the conventionally treated group was bleeding from multiple gastric erosions, and died.

TABLE V.—*Recurrent Haemorrhages in Hospital*

	No. Treated	No. of Recurrences					
		1	2	3	4	8	Total
Conventionally treated ..	53	6		1	1	1	9 (21)
Drip treated	100	8	6	1	1		16 (27)

Patients' Views on Treatment

Few patients objected to the technique. Those who had had previous treatment of haemorrhage preferred the milk drip, particularly if the former treatment included a few days of restricted diet. They looked and felt confident and reassured on their second day. Confidence was often enhanced by seeing others in the same ward undergoing the same type of therapy. Some complained of mild nasal irritation and soreness of the throat, not severe enough to warrant discontinuation of treatment. By the end of the first week this complaint became more frequent, and at this time it was usual to discontinue the drip but to maintain it at night for a further week. If there had been recurrent bleeding or if occult blood persisted in the stools the drips were continued for longer periods.

Patients could tolerate the drip for periods of six weeks. A few, asked to write down their impressions, even referred to a soothing effect of the steady flow. One man and one woman objected initially: the woman had objected to other forms of therapy; the man was old and querulous at 71 years. Two other women would not have the tube replaced after the fourth or fifth day. One of these had three recurrent bleeds but could not be induced to change her mind.

Views of Medical Attendants on Treatment

The doctors and nursing staff were impressed by the apparent well-being, reassurance, and confidence of the 84 patients out of the 100 who did not bleed again or who were not moribund on admission. The patients were propped up on the second day, taking generous meals in addition to the milk drip, looking and feeling comfortable. Sweating and anxiety were the exception, pulse and blood pressure had usually been restored. Their condition was in notable contrast to that of patients treated by initial starvation, and a further improvement on the state of those treated by early feeding without continuous milk drip. The 16 who bled again were more distressed, as the rejection of their tube with a bloody vomitus, sometimes repeated, would impair confidence. Nevertheless eight of these resumed their drip and progressed steadily to recovery. Some of the patients' minor discomforts might have been relieved by the use of the latex tube, advocated by Woldman (1936). It is unfortunate that the treatment is difficult to establish in elderly people with early recurrent haematemesis, as the danger lies with this group.

In only one patient, a man with an aneurysm of the splenic artery in the base of a large gastric ulcer, who died suddenly with massive bleeding, may the use of the tube have aggravated the haemorrhage.

Conclusions

The results are given of the treatment of 153 ulcer patients admitted to hospital as emergency cases for haematemesis or melaena. Of these, 100 were treated with a continuous intragastric milk drip given from the time of admission, and 53 were treated as a control group by one-hourly milk feeds and early generous step-up regimes. The drip-treated group received purées from the first or second day. Both groups were adequately transfused. The therapy does not prevent the occasion for surgery with continued bleeding in old people, nor has it so far produced a fall in the mortality of this group.

There was a tendency to diminished duration of bleeding in the drip-treated group. More than two recurrent bleedings in hospital were very uncommon in this group, but the numbers of recurrences under treatment do not differ significantly in the two groups.

The drip-treated group displayed earlier reassurance, confidence, and freedom from shock than the control.

Continuous milk-drip therapy for peptic ulcer haemorrhage can be carried out in hospital for periods of two or more weeks without inconvenience to the patient.

It can be affirmed that this is a safe treatment comparable in results to one-hourly feeding and transfusion regimes.

We would like to express our thanks to Dr. C. N. Armstrong for permission to include in the present series patients admitted under his care at the Queen Elizabeth Hospital, Gateshead.

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STANDARDS OF FITNESS AMONG DRIVERS OF COMMERCIAL VEHICLES

A SOCIO-MEDICAL INVESTIGATION BASED ON WARTIME RECORDS OF CIVILIAN MEDICAL BOARDS

BY

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A recent lecture by the senior medical officer of the London Transport Executive describes in detail the steps taken to ensure that the drivers of London's motor-buses are healthy when recruited and maintain a satisfactory standard of fitness throughout their period of service (Norman, 1954). This leads one to consider what comparable steps are taken with reference to other professional drivers. So far as public service vehicles are concerned, the precautions taken seem to be adequate. The licensing authority, before granting permission to drive a bus or a coach, requires the applicant to have a general medical examination (including tests of vision) and to pass a special driving test. Many of the larger bus companies, including London Transport, conduct their own medical examinations and have even higher standards of vision and health than the statutory licensing authorities.

In contrast, *no* medical test is required of drivers of commercial vehicles, and inquiries into their fitness to drive are both limited and ill-defined. Whatever the type of vehicle may be—and it may be anything from a three-wheel van to a five-ton lorry—the applicant for a licence has merely to answer four questions regarding the state of his health and declare the answers to be true. The four questions (which appear on all driving licence forms) are well known:

1. Do you suffer from epilepsy or from sudden attacks of disabling giddiness or faintness?

2. Can you read at a distance of 25 yards in good daylight (with glasses if worn) a motor-car number plate containing six letters and figures?

3. Are you without either hand or foot or are you suffering from any defect in movement, control, or muscular power of either arm or leg?

4. Are you suffering from any other disease, mental or physical, or disability which would be likely to cause the driving by you of a motor-car to be a source of danger to the public?

Question 2 is checked by the examiners who conduct the official driving tests. They would presumably also notice so gross a defect as absence of a limb. Otherwise the physical competence of an applicant for a driving licence depends on his truthfulness, his knowledge of his own health, and the construction he puts on the phrase "likely . . . to be a source of danger." Medical men frequently experience difficulty in convincing patients that they are no longer fit to drive, and know that (if they choose) even persons who are obviously a danger to the public can ignore their advice.

At a meeting of the Royal Society of Medicine a doctor stated that one of his elderly patients "who drove a high-powered car at reckless speed" was extremely annoyed at the advice that he should give up driving after he had had three blackouts in one year and had been found to have developed petit mal (Crosby, 1953). On another occasion, a neurologist deplored the number of epileptic and paralytic patients who drive cars, and added, "The patient in every case considers himself entirely fit to drive" (Campbell, 1952).

Present Investigation

To amplify the evidence of these isolated instances the civilian medical board records of 1,276 men who earned their living as drivers of road vehicles were scrutinized. The records, which were compiled during the years 1941–4, were drawn from three areas† and referred to 761 lorry drivers, 406 drivers of vans or other light commercial vehicles, 31 drivers of public service vehicles, and a miscellaneous group of 78 chauffeurs, drivers of ambulances, and A.A. men.

TABLE I.—*Professional Drivers of Road Vehicles*

Reasons for Rejections	Lorries	Vans	P.S.V.	Other	Total
Eyes:					
High myopia	3	4		1	8
Pathological defects	2				2
Ears:					
Defective hearing	5	2			7
Pathological conditions	6				6
C.N.S.					
Epilepsy + unconsciousness	3	1		1	5
Neurological conditions		2			2
Mental defectiveness	4				4
Mental instability	3	3			6
Skeletal:					
Upper limbs	3	3		1	7
Lower limbs	12	9	2	4	27
Other skeletal defects	3	2		1	6
Cardiovascular:					
Heart disease	11	4		1	16
Hyperpiesis	2	2		3	7
Varicose veins	7	2			9
Lungs:					
Tuberculosis	5	10	1		16
Chronic chest conditions	6	5			11
Abdominal:					
Peptic ulcer	10	9		1	20
Hernia	7		1	1	9
Other		1			1
General:					
Diabetes	2			1	3
Other endocrine disorders		2			2
Skin conditions	2				2
Other	5	1		1	7
All disabilities	101	62	4	16	183
No. of men examined	761	406	31	78	1,276
Rejection rate	13%	15%	13%	20%	14%

Of these 1,276 men, 28% were under 20 years of age, 43% were between 20 and 34, and 28% were between 35 and 45. At the end of the medical examination each man was graded according to his general standard of fitness. Briefly these grades were: (1) fit for all forms of military service; (2) minor or remediable defects; (3) fit for light duties only; and (4) not fit for any form of military service. In practice men in Grades 1 and 2 were called up for national service, and men in Grades 3 and 4 were rejected. Ninety-nine of the professional drivers were placed in Medical Grade 4 and 83 in Medical Grade 3, making a total rejection rate of 14%. The main reason for down-grading was identified in every case, and the results are summarized in Table I.

*In receipt of a grant from the Medical Research Council.

†Essex, 577; Leicester, 273; Northampton, 426.

Needless to say, the records of the men who were rejected did not specifically state that the examinees were not fit to drive. It is apparent, however, from what was discovered at the civilian medical board examination that the four questions on the standard driving licence form had, either intentionally or from lack of medical knowledge, been incorrectly answered by several men. Thus question 1 (epilepsy) should have disqualified 5 of the group, a further 49 were either unaware that they had defective eyesight or had chosen to hide the fact, and 34 had failed to state that they were suffering from defects of "movement, control, or muscular power" (provided, that is to say, none of the men were holders of "cripple" licences).

The fourth question on the driving licence form is extremely difficult for anyone to answer correctly. For, besides assuming a lively social conscience on the part of every applicant, it demands much more medical knowledge than most people possess. Even members of the medical profession are not unanimous about which diseases should be described as "likely to cause the driving of a car to be a source of danger to the public." Dr. Norman, for instance, considers that any condition that may cause either momentary attacks of unconsciousness or giddiness, or increased liability to fatigue, is potentially dangerous. If this is the standard of health expected for all professional drivers of road vehicles, then none of the national service rejects should have been holding a driving licence. For, whatever the nature of their complaints, the fact that they had (in the middle of a war) been found unfit to serve in the armed Forces was a sure indication that they at least suffered from "increased liability to fatigue."

If, however, a lower standard of health is acceptable then an arbitrary selection of the diseases which apply to the fourth question would have to be made. If, for instance, it is considered that only pathological conditions of the eyes, deafness, mental defectiveness, and instability, neurological disorders, diabetes, and cardiovascular diseases (other than varicose veins) are "likely . . . to be a source of danger to the public," then only 53 of the 172 men who were rejected need have answered the fourth question in the affirmative. Even so, the total number of drivers who fell below the (presumed) standard of fitness for holders of ordinary driving licences would be 143, or one in eleven of the total group.

Vision (Table II)

Included in the civilian medical board examination was a vision test, based on the well-known Snellen type, and performed, if necessary, with or without spectacles. An ophthalmologist's report was obtained in all cases of eye disease and for all men whose corrected vision failed to reach either 6/12:6/12 or 6/6:6/36 Snellen type. Some of the drivers with defective vision did not wear spectacles and others were not fully corrected by the spectacles they were wearing. Thus there were three men with 6/60:6/60 who had no spectacles, four who had 6/60:6/36 after correction, and four whose good eye could not be improved beyond 6/24. The overall rate for standards *below* the one regarded as safe for driving was 3.8%.

TABLE II.—*Visual Standards Among 1,276 Professional Drivers*

Below Standard Required for	Lorry	Van	P.S.V.	Other	Total
P.S.V. licence*	31	15	—	3	49†
L.T.B. (re-employment)‡ ..	66	28	1	4	99
L.T.B. (initial employment)‡	103	63	4	8	178
	13·5%	15·5%	16·1%	19·3%	14·0%

* That is, Snellen type 6/12: 6/36, or ability to read a motor-car plate at 25 yards.
† Including 8 men with severe myopia (6/60 both eyes) and 22 who were blind in one eye.
‡ The corresponding figures include men who would have failed the easier tests.

The standards of vision required by the London Transport Board at their initial and re-employment examinations are respectively 6/9:6/12 (without spectacles) and 6/9:6/36 (with spectacles). This means that 178, or 14%, of the men examined by the civilian medical boards would not have obtained employment as a London bus driver and 99, or 8%, would, in spite of being experienced drivers, have been transferred to other jobs.

Types of Vehicles.—The all-causes rejection rate was highest for the miscellaneous group and lowest for the drivers of public service vehicles, but the difference between these men and the group of lorry drivers was marginal. Failure to reach the licensing authority visual standard was roughly the same for lorry drivers, van drivers, and men in the miscellaneous group, but there were no drivers of public service vehicles with vision below 6/12:6/36.

Accidents Due to Commercial Vehicles.—For the two years 1948 and 1949 the Registrar-General has analysed 7,999 deaths on the road by victim and vehicle involved (Registrar-General, 1950, 1951). From this analysis it appears that the number of pedestrians and pedal-cyclists killed in road accidents was 5,541 (see Table III). Of these

TABLE III.—*Analysis of 7,999 Deaths on the Road by Victim and by Vehicle Involved*

Vehicles involved, other than that Carrying Victim	Victim was: On Foot	On Pedal Cycle	On Motor-Cycle	In Private Car	In Bus	In Motor Goods Vehicle	In Other Type of Vehicle	Total of First 3 Cols.
Goods transport vehicle*	1,568	471	375					(2,414)
Bus, tram or train ..	702	167	72					(941)
Private car ..	1,190	394	245					(1,829)
Motor-cycle ..	247	35	42	326	19	137	125	(324)
Pedal-cycle ..	164	37	24					(225)
Coaches and taxis ..	129	29	16					(174)
Other vehicles	63	13	27					(103)
No other vehicle	—	332	477	179	142	247		(909)
Total ..	4,063	1,478	1,278	505	161	384	125	(6,819)

* In 1954 there were 945,127 licences issued for goods transport vehicles.

2,039 were knocked down by goods transport vehicles, 865 by buses or trams, and 158 by coaches or taxis. Thus, in more than half of the pedestrian and pedal-cyclists' deaths, the mechanically propelled vehicle was in charge of a professional driver.

Discussion

Compared with men in other occupations, the percentage of physically defective drivers is slightly below average (Stewart, Webb, and Hewitt, 1955). But, considered in relation to the number of licences issued annually to goods transport vehicles (just under one million in 1954), it suggests that there are—not counting private-car owners—a formidable number of potentially dangerous drivers on the roads. It is possible that some of the men who were examined by the civilian medical boards had applied for, and been given, the special licences issued to physically defective people. There may also have been a number of cases where driving experience outweighed other deficiencies, for opinion varies on how much different defects affect a man's competence as a driver. Nevertheless, the fact remains that the final decision in this matter rests not on an unbiased assessment of fitness, but with the man who is applying for a licence. Whether or not he passes as fit depends entirely on his veracity, his self-knowledge, and his ability to answer certain difficult medical questions. In these circumstances there is nothing to prevent a man with a serious defect (or vision that has deteriorated to danger levels since he first passed his driving test) from driving a heavy lorry to the public danger. Civilian medical board records support the view that this source of public danger actually exists.

Viewed from the angle of road safety, we cannot afford to be complacent about the fact that the percentage of physically defective men who earn their living as drivers is not exceptionally great. There should be no such men.

Those interested in reducing the appalling number of deaths on the road might do well to press for a radical revision of the present system of granting driving licences to professional drivers.

Summary

Civilian medical board records of 1,276 professional drivers were examined for causes of rejection from military service. Physical defects and impairment of vision found were considered in relation to the declaration of physical fitness made on the application form for a driving licence.

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HYDROCORTISONE OINTMENT IN THE ECZEMAS

BY

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Cortisone has been used with dramatic effect in diseases of the skin. Unfortunately, the side-effects of cortisone therapy are hazardous and limit its use in dermatological practice to potentially fatal illnesses such as pemphigus, disseminated lupus erythematosus, and exfoliative dermatitis. The local application of cortisone has little or no anti-inflammatory effect on the skin, though it has been of value as an ophthalmic application, being readily absorbed through the conjunctiva.

Hydrocortisone has been found to exert anti-inflammatory effects when applied to the skin as well as when administered systemically. No systemic effects have been reported in the hundreds of patients who have used hydrocortisone ointment, and Smith (1953) found no significant change in the circulating eosinophil count when ointment containing 150 mg. of hydrocortisone was applied to normal or diseased skin.

Literature

Sufficient reports on the use of hydrocortisone ointment have been published for some assessment of the type of case in which it is of most value. With one exception (Goldman and Preston, 1953) the accounts have been enthusiastic.

There is general agreement that the ointment is of no value in psoriasis, lichen planus, pemphigus vulgaris, generalized exfoliative dermatitis, and alopecia areata. Evidence of the response of chronic discoid lupus erythematosus is conflicting; Sidi and Bourgeois-Gavardin (1953) report improvement or healing in seven cases, while Sulzberger *et al.* (1953) found only slight improvement in one of five cases, and other observers have observed the same lack of response.

The effect of hydrocortisone ointment in atopic eczema has been extensively studied (Sulzberger and Witten, 1952; Sulzberger *et al.*, 1953; Robinson, 1953; Sidi and Bourgeois-Gavardin, 1953; Malkinson and Wells, 1954; Witten *et al.*, 1954), and the results have shown a remarkable uniformity, about two-thirds of the cases responding in each series. McCorriston (1954), in a series of 104 cases, obtained even better results and records a good response in each case. Most observers found that response was apparent within a week and that benefit was sometimes visible within 24 to 48 hours from the beginning of treatment.

Several series were controlled by the use of the "symmetrical paired comparison" method, and it was noted that some improvement often occurred on the side of the body on which the inert ointment was used. Also in cases using hydrocortisone on one area only, improvement was observed in remote areas. Systemic absorption or contamination with hydrocortisone has been suggested as the cause, but a more likely explanation is the "sympathetic" improvement which is also seen with other forms of local treatment.

McCorriston found that 60% of cases of atopic eczema maintained improvement on stopping treatment, but others (Robinson, 1953; Malkinson and Wells, 1954) have observed a relapse in most cases, or even an exacerbation.

The treatment has been found most effective in eczema or dermatitis affecting the eyelids, pinnae, and ano-genital regions (Sidi and Bourgeois-Gavardin, 1953; Alexander and Manheim, 1953; Malkinson and Wells, 1954), probably because of improved absorption from these areas. Acute contact dermatitis, lichen simplex, nummular eczema, and seborrhoeic dermatitis are also reported as responding to hydrocortisone ointment. Sidi and Bourgeois-Gavardin (1953) warn against the danger of secondary infection in acute contact dermatitis; they also state that the anti-pruritic effect is slight in cases in which much lichenification is present.

The American work has been criticized on the grounds that the patients were selected private patients who knew they were having some special remedy applied. In the present series the patients were hospital patients who were aware that they were receiving a special remedy, and the control cases were, of necessity, under a similar impression. Those patients were selected whose diagnosis was firmly established and in whom the areas affected were not too extensive.

Method

A series of 105 cases of various types of eczema and dermatitis were treated with an ointment containing 1% hydrocortisone acetate; in a few of the more resistant cases 2½% hydrocortisone was used. The base consisted of anhydrous lanolin, petrolatum, and mineral oil ("cortef" ointment).

A further 23 cases of eczema were used as controls, at the beginning of the trial alternate patients being issued with the ointment base in a similar packing and given the same instructions.

Patients were instructed to use a thin smear of the ointment twice daily, to avoid soap and water on the affected areas, and to use liquid paraffin or olive oil for cleaning.

Results

Nummular Eczema.—This was separated from other endogenous forms of eczema on account of its distinctive pattern. Of the 25 cases treated, 18 had had previous treatment with *x* rays and tar preparations without healing. Ten healed completely, most within one week, 11 improved but did not heal, three showed no response, and one became worse under treatment. Five cases which had healed or improved relapsed within seven to ten days of stopping treatment. Three of the 10 controls showed some improvement, and the remaining seven became worse.

Eczema.—This group contained an assortment of cases of eczema which were considered to be endogenous and which affected various areas of the body. Of the 24 patients treated, 17 had had previous treatments without healing. Eight healed completely, eight improved, three showed no response, and five became worse; one of the last-named appeared to be aggravated by the ointment. Of the six controls, one healed, two remained static, and three became worse. Half of those not responding to treatment had

eczema of the hands which involved the palmar surface, and it seems probable that lack of penetration of the thickened horny layer may have contributed to failure. In another of the failures, infection, which was present when treatment began, spread rapidly. Of the cases which improved, four relapsed within seven to ten days of stopping treatment.

Atopic Eczema.—This group comprised 30 patients varying in age from 1 year to 50 years. Twenty-five were old patients, the majority of whom had been difficult to control with the usual treatments. Three patients were treated during admission to hospital. Nine healed completely, 13 improved, six showed no response, and two became worse. Of the four controls, three showed no response and one became worse. Most of the cases which responded to treatment showed maximum improvement within a week. The more lichenified and chronic the eczema the less effective was the treatment, and in these resistant cases 2½% hydrocortisone ointment did not seem to be more effective than the 1% ointment.

Lichen Simplex.—Of the 10 patients treated, nine had very long-standing lesions which had resisted the usual occlusive and *x*-ray therapies. Three healed completely after three to four weeks of treatment, and have remained healed. Three improved and gained relief from itching, but despite the use of 2½% ointment their lichenified patches remained, to be scratched again when treatment ceased. Four showed no response to 2½% ointment. Of the three controls, two became worse and one remained static.

Contact Dermatitis.—Six new cases of acute and weeping contact dermatitis were treated. All were due to medicaments. One did not respond. Improvement in the others was dramatic, the lesions drying and subsiding almost completely within two to three days.

Pruritus Ani.—Ten cases of pruritus ani were treated; six of them had resisted various therapies, including *x* rays. Four healed and remained symptom-free, four improved but did not lose all their irritation, and two derived no benefit. No controls were included in this series, and it is recognized that a fairly high proportion of these cases derive benefit from any new treatment. Nevertheless, knowing the chronic cases which admitted improvement, one is impressed with the therapeutic effect.

Comment

Improvement or complete healing was observed in 76% of the 105 treated cases and in 17% of the 23 controls. Deterioration occurred in only 7.5% of the treated cases and in 56% of the controls. It is evident that the psychological effect of the "new treatment" (packed in impressively small 5-g. tubes) was slight. Although there was an overall high rate of improvement certain conditions improved more readily than others.

Those which improved most rapidly were cases with a raw weeping skin lesion which allowed rapid absorption of the hydrocortisone. Acute contact dermatitis responded dramatically and almost healed in two or three days. Two of the treated patients presented with an acute weeping dermatitis of the face a few days before they were due to go for their summer holiday. With the usual bland applications recovery might have taken 10 to 14 days. In three days after application of hydrocortisone the rash was almost healed in each case and these patients did not miss their holiday.

A high proportion of cases of nummular eczema healed completely in a week; and here, too, the more acute and weeping the eczema the better the response. Relapse followed cessation of treatment in some cases, but application of a minute amount of ointment every day, or even every second to third day, was sufficient to prevent recurrence. In some cases healing was not complete, but hydrocortisone was useful in rapidly controlling exudation and rendering the eruption suitable for applications of tar pastes.

Patients suffering from an acute skin eruption may be prepared to endure messy applications with the prospect of recovery in sight, but the atopic eczema subject spends a lifetime fighting unpleasant attacks of eczema with almost equally unpleasant remedies. The freedom from sting, stain, and stench (as Sulzberger puts it) makes hydrocortisone a welcome treatment for the "atopic." Unfortunately the results are variable and unpredictable. Some cases healed completely in less than a week and derived complete relief from itching. Others improved more than with any other local application. Healing or improvement occurred in two-thirds of the cases treated. Those which did not respond well had very lichenified eczema that was not easily penetrated by the ointment. Patients in whom excoriations were more marked than eczema did not respond well, possibly because their scratching had become a habit. In some of the milder cases the patients still complained of itching, though the skin had apparently returned to normal; this may explain the continuation of scratching. Infection tended to be spread by the ointment, and should be regarded as a contraindication until it has been controlled by appropriate antibiotic therapy. The types of eczema outlined can easily be recognized and hydrocortisone avoided in these cases, but there remained in this series a few cases which were not improved by the ointment, though clinically indistinguishable from cases in which it worked like a charm.

Most cases of atopic eczema relapsed when treatment was stopped. It has been suggested that 2½% hydrocortisone ointment may be useful for controlling the eczema and that 1% can be used for maintenance therapy. In this series it was found that cases either responded to 1% ointment or not at all. Maintenance therapy is possible, but may prove expensive when large areas are affected. Once the rash was controlled the patient could revert to the usual tar applications with every hope of maintaining improvement; only when treatment was stopped completely was there a severe relapse. It seems likely that hydrocortisone may prove most useful as something on which the atopic eczema subject can rely to control the exacerbations to which he is so prone. The very knowledge that he has this weapon available will probably make its use less often necessary.

In other cases of localized areas of eczema the results depended largely on the site and nature of the eruption, raw and exuding areas responding well to treatment and lichenified chronic cases deriving little benefit. Eczema of the hands which involved the palmar surface responded poorly, presumably because of lack of penetration of hydrocortisone through the thickened horny layer.

Similarly, lack of penetration probably explains the poor results in lichen simplex. The 2½% ointment was used on all cases, and treatment was maintained for three to eight weeks, but only 30% of the cases healed.

In pruritus ani the degree of improvement depended on the extent and nature of the perianal dermatitis. Those patients with an active eroded and excoriated eruption experienced rapid relief, which in several chronic cases proved lasting. Those with much lichenification derived some relief from itching but did not heal. Persistent cases with intractable itching but with little or no abnormality of the skin did not respond to hydrocortisone therapy, presumably because the site of origin of their irritation was in the head rather than the seat.

From these results it is evident that hydrocortisone is not the complete answer to the treatment of eczema and dermatitis. It is, however, a potent weapon whose value can be compared to that of *x*-ray therapy, provided that it is used with the same circumspection.

Summary

A series of 105 cases of eczema and dermatitis were treated with 1% and 2½% hydrocortisone ointment. A further 23 cases were treated as controls with an inert ointment. Improvement or healing occurred in 76% of the treated cases and in 17% of controls.

Response appeared to depend on the ease of absorption of hydrocortisone, eroded and exuding eczema and dermatitis healing rapidly, while lichenified eczema showed little improvement.

Good results were obtained in acute contact dermatitis, nummular eczema, atopic eczema, and perianal dermatitis. Lichen simplex, lichenified atopic eczema, and lichenified cases of ano-genital pruritus responded poorly. Infection was spread by the ointment unless controlled before its use.

Relapse occurred in many chronic cases on stopping treatment, and could be prevented by using the ointment less frequently as maintenance therapy or by reverting to the use of tar applications.

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A SEARCH FOR ABNORMAL HAEMOGLOBINS IN SOME SOUTHERN SUDANESE PEOPLES

BY

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Sickle-cell Tests

Nilotic peoples are found in two main areas—the southern Nilotes in Uganda and round the eastern shores of Lake Victoria, the northern Nilotes in the Southern Sudan. During the course of investigations among the northern Nilotes of Upper Nile Province, Sudan, the blood of a large number of individuals was examined for sickling. Some specimens were sent to laboratories for testing; in London, where positive specimens from West Africa could be used as controls, 344 specimens were tested, 83 by one of us (H. L.) and 261 by Dr. J. N. M. Chalmers, of St. George's Hospital; in Khartoum 215 were examined by Professor Dean Smith of the Kitchener School of Medicine.

These specimens were obtained from unrelated adult individuals; details of the sampling methods employed are given elsewhere (Roberts, Ikin, and Mourant, 1955). In the field, testing was largely restricted to specimens from children, 10 adults and 170 children of all ages being examined by D. F. R.; these children constituted the major part of the child population of one Dinka and two Shilluk villages, and the individuals from each village were therefore not all unrelated. As regards technique, in London and in the field, 2% solutions of potassium metabisulphite were used, freshly made up on each occasion with distilled water; in Khartoum, each specimen was carefully enclosed bubble-free under a coverslip ringed with petroleum jelly, and examined after 24, 48, and 72 hours.

Altogether specimens from 739 individuals were examined, representing the different indigenous peoples as follows:

People	Adults	Children
Northern Dinka	217	103
Shilluk	204	67
Nuer	100	
Mabaan	34	
Dinka/Shilluk/Nuer-hybrids ..	14	

Since in no individual of this large sample was the sickle-cell trait observed, it is concluded that the absence of the trait is a characteristic typical of the northern Nilotic peoples. This finding is similar to that of Foy *et al.* (1954).

Examination by Electrophoresis

Seventy-five specimens were further examined by paper electrophoresis according to the procedure described by Lehmann and Smith (1954). Of these, 64 specimens were from northern Dinka individuals, 4 were from Mabaan, 3 were from Dinka/Nuer hybrids, and 4 from Dinka/Shilluk hybrids.

All blood specimens contained nothing but normal adult haemoglobin. No haemoglobin S (or D), C, E, or G was found. The results of this survey are in striking contrast to those obtained in the Gold Coast (Edington and Lehmann, 1954a, 1954b), where out of 211 West Africans examined 41 were found to possess haemoglobin S, 29 haemoglobin C, and 1 haemoglobin G. On the other hand, in Tanganyika (Dar es Salaam) 100 out-patients of mixed tribal origin but mainly Bantu were recently examined by us through the kindness of Dr. Mackey; although 12 individuals with a haemoglobin showing the electrophoretic properties of S were noted, no haemoglobin C or any of the other known variants was found.

Discussion

In several recent publications the view has been advanced that the sickle-cell gene provides an example of balanced polymorphism in man. Neel (1953) discussed the possibility that the balance was attained through increased fertility on the part of the heterozygote. Allison's (1954a, 1954b, 1954c) experiment in Kampala, and his examination of the geographical distribution of the sickle-cell trait in East Africa, with high and low frequencies respectively confined to endemic and non-endemic malarious areas, provide some evidence, implementing that of Brain (1952), Mackey and Vivarelli (1952, 1954), and others, that possession of the trait confers selective advantage in malarious regions. He postulates a condition of balanced polymorphism, selection acting against the sickling homozygote through sickle-cell anaemia, against the non-sickling homozygote through malarial susceptibility, the heterozygote, however, being at an advantage over both homozygotes through the protection afforded by the sickle-cell trait against malaria, especially subtertian.

The role of malarial endemicity in determining sickle-cell frequency once the gene is introduced, however, should not be exaggerated. Many tribal areas are not sufficiently local in extent to be assigned to a single category of endemicity: the range of flight of the mosquito may admittedly be greater than the limit of several hundred yards generally quoted; but it is essentially local, and many "hyperendemic" tribal territories must consist of intensely malarious and less malarious districts. Hence differences in selection pressure will occur within the territory, and if mating tends to be to any extent local differences in gene frequency will result. The actual value found for any sample will depend on a combination of social and ecological factors, the mating system of the people, the

length of time their economy requires individuals to spend in malarious areas, and the intensity of malarial infection in those areas. From these considerations it would seem that Allison's (1954b) attempt at a geographical analysis by means of a simple table is not sufficiently detailed to be convincing. Nor should the degree of selection pressure be overestimated. If, as is generally recognized (Taliaferro, 1949), malarial immunity is of two types, innate and acquired, then presumably the hypothetical immunity given by the sickle-cell trait falls into the former category. Is the non-sickling homozygote in endemic areas not protected to some extent by acquired immunity? Too little attention has been given to established work on malarial immunity during recent developments in this field.

Undoubtedly the functional approach to the problem of the sickle-cell trait represents a stimulating advance on the purely descriptive. The unequivocal establishment of this first example in man of balanced polymorphism would represent a considerable advance in anthropological theory. Hence the importance of clarifying the several points weighing against outright acceptance of the hypothesis in its present form.

As Edington (1953, 1954) and Lehmann (1954) have pointed out, the assumption that the simple homozygous theory of the inheritance of sickle-cell anaemia is correct remains difficult to accept completely. There are other factors to be considered; for example, those relating to the proportions of different haemoglobins such as are noted above, of which little is yet known. Certainly in areas where haemoglobin C exists, sickle-cell crises must occur in individuals heterozygous for S and C; and malarial infection, since it may precipitate such crises, may thereby adversely affect the proportion of heterozygotes. Some advantage of the non-sickling homozygote over sickling individuals could indeed be postulated to explain the several studies noted by Neel (1950), in which the sickle-cell frequency appeared to dininish with age, though other explanations can be advanced.

The assumption that malarial susceptibility is proportional to malarial mortality is not necessarily correct. As regards the demographic situation, Christophers (1949) concluded that in indigenous tropical populations "no obviously greater infant and child mortality rate accrues under hyperendemic conditions [of malaria] than is generally normal apart from malaria."

Neither Moore *et al.* (1954), in two samples, nor Edington (1954) in two samples, have been able to confirm any association between parasite rate and sickling such as is claimed by Allison (1954a) on a barely significant test of data relating to Baganda children; nor does either of Beet's (1946, 1947) investigations show any significant association; when the aggregate of the seven sets of data published by these authors is considered no significant relationship emerges. It should be pointed out that the χ^2 values given by Allison (1954a), if calculated by recognized procedures, are all incorrect; using Fisher's method with Yates's correction for continuity, χ^2 values of 1.64, 3.64, and 4.05, each with one degree of freedom, should replace those of 19.3, 4.1, and 5.1 calculated by Allison. In Raper's (1954) recent sample of 1,675 children, among those in the second year of life there was a significantly lower malarial rate in sicklers, but at no other age nor in the whole series was this association shown. It appears, then, that sickling has no effect on parasite rate in adults, though it may have an effect during a very limited period in early infancy. It is thus difficult to accept without further confirmation Allison's results on Luo adults, where in only 2 out of 15 adult sicklers, but in 14 out of 15 adult non-sicklers, malaria parasites were observed after repeated artificial inoculation. On each of the above points the evidence is unfortunately limited.

The findings reported here concerning the northern Nilotes, however, are not equivocal. Among the Shilluk, Dinka, and Nuer, by reason of their ways of life and the nature of their habitats, malaria is endemic. The Shilluk are a riverain people; they make more use of the rivers for purposes of communication than do the Dinka: most of their villages are within a few hundred yards of the river, and a number are actually at the waterside. Most Dinka and Nuer spend the dry season by the rivers, and the wet season, when swamps abound, in inland villages. Malaria incidence would be expected to be at its lowest for the Dinka in the early dry season when the swamps inland have dried but immediately before the depletion of water in their wells, waterholes, and "hafirs" (waterholes of human construction) necessitates the movement of cattle and humans to the rivers. In a Dinka inland village, during the week before the move to the riverside cattle camp, out of a total village population estimated at 350, 11 individuals (3.1%) were seen to be suffering from a fever seemingly malaria, which responded to treatment with mepacrine: from only one of these individuals, unfortunately, could blood smears be obtained, in which instance M.T. rings were observed.

In the absence of published data concerning malaria in these peoples, the opinions of two authorities are quoted. Professor P. C. C. Garnham, of the London School of Hygiene and Tropical Medicine, states (personal communication) that "there is no doubt that the malaria incidence is very high in the Southern Sudan near Malakal." Dr. G. J. Clark, Province Medical Inspector, Malakal, states (personal communication) that new cases attending the out-patient department of Malakal Hospital for the year 1953–4 included 2,605 malarial cases, some 2% of the total, though many more were diagnosed as malaria which were either not proved or were probably relapses; that the majority of proved cases were *P. falciparum*, there being 2,488 positive M.T. slides; that malaria is endemic in the Malakal region; and that its incidence is reckoned to be greater than in the Nile region of Equatoria Province (where considerable frequencies of the sickle-cell trait occur).

Hospital figures are of course not representative of these primitive populations, since only a small proportion of individuals ever reach hospital; malarial cases are adequately treated at the outlying dispensaries, whereas more serious cases are sent to hospital; yet in the majority of many villages visited during the present investigation clinical malaria appeared to be the most frequent complaint. Thus all the evidence points to a high malarial endemicity in the region. This group of northern Nilotes, then, provides one exception to Allison's statement that "the world distribution of the trait is also in accordance with the view presented"—namely, the relationship of the sickle-cell trait to malarial endemicity. There are other exceptions. The sickle-cell trait is absent from aborigines of Malaya despite the high malarial incidence (Polunin, 1953); and the trait is virtually absent in the Union of South Africa. Budtz-Olsen and Burgers (1955) have tabulated surveys of nearly 6,000 Africans from that area, and have pointed out that at least in Zululand malaria has been present for generations.

Anthropological Interpretations

The differences noted here between West Africans and Nilotes in frequency of abnormal haemoglobins other than S suggest that further investigations may yield information of considerable anthropological interest. Haemoglobin E, for example, first found in a child of an Asian father (Itano *et al.*, 1954), has also been found in Siamese (Chernoff *et al.*, 1954) and in the Veddas of Ceylon (Graffe *et al.*, 1954), but not in the limited number of Africans so far examined.

As regards S haemoglobin, the present unresolved state of the hypothesis of marked association between sickling and malaria necessitates dual attempts at anthropological interpretation of the sickle-cell findings of the present survey.

If the hypothesis of balanced polymorphism associated with malaria is correct, then with this observed incidence of malaria the sickle-cell trait ought to be present among the northern Nilotes. To explain its absence, two suggestions may be offered. There may be insufficient malarial

mortality of the non-sickling homozygote in these peoples to raise the frequency of the gene if introduced—that is, there may be other genetic factors besides sickling which protect against death through malaria. Alternatively, the gene may never have been introduced (by mutation or intermarriage with individuals from populations possessing the sickle-cell) among the northern Nilotes. Had they received it, then selection would have increased its frequency to that at which equilibrium occurred, its diffusion among these peoples being broadened by their mating systems: the increase in gene frequency would have been rapid at first, since its introduction would presumably be in the heterozygous condition, matings between heterozygotes would occur much more rarely than between heterozygote and non-sickling homozygote, and the sickling homozygote would therefore in the initial stages very rarely be produced; loss of the gene in appreciable quantities would only occur after its frequency had reached such a level that heterozygotes were mating.

The finding by Foy *et al.* (1954) of the sickle-cell trait in one or two individuals among the southernmost groups of the northern Nilotes suggests that the gene is only now beginning to enter this region from the south. Certainly such Shilluk as migrated to their present territory from the south could not have brought the gene and subsequently lost it. Nor could the southward-moving Lwo groups, who according to Crazzolara's reconstruction of traditions subsequently became the peoples known to-day as the central and southern Nilotes, have taken the gene with them when they diverged from the northern Nilotic peoples. Since the southern Nilotes now possess the trait in appreciable frequencies (Lehmann and Raper, 1949; Foy *et al.*, 1954; Allison, 1954b), they must have received it at a date later than that at which they diverged from the northern groups.

If, on the other hand, the postulated selective advantage under malarial conditions of the sickle-cell trait should prove to be more apparent than real, then the presence of the trait among the southern Nilotes would seem to be due to hybridization with peoples of high sickling frequency in the areas to which they wandered. On this hypothesis, the alternative explanation for the difference in sickling between northern and southern Nilotic groups—that a northward-moving Shilluk group possessing the gene interbred with non-sickling groups in their new territory, with subsequent dilution of the gene frequency—seems less feasible, since in this instance the gene would be expected to occur at low frequency among the northern Nilotes, which the data do not show.

The above discussion shows clearly the increase in anthropological interest that may accompany increased knowledge of a particular gene. Whatever the explanation, the sickle-cell trait to-day is a physical criterion distinguishing between the northern and southern Nilotic groups, being absent in the former and present at medium frequency in the latter. Some degree of genetic divergence is thereby implied—less if the trait is selectively advantageous, greater if it is not.

Summary

No abnormal haemoglobin was discovered by paper electrophoresis of 75 blood specimens from northern Nilotes of the Southern Sudan. In 739 specimens examined no sickling was found. These findings suggest that the association between malaria and sickling is more complex than might at first appear; their anthropological significance is discussed.

We acknowledge the practical assistance given by Dr. J. N. M. Chalmers and Professor D. Smith in the examination of the specimens; the help and interest of Professor P. C. C. Garnham and Dr. G. J. Clarke; and, in Khartoum, the technical assistance of Miss K. Dobbins and Mr. L. B. Greenhalgh through the courtesy of Professor H. V. Morgan.

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A SURVEY FOR HAEMOGLOBINS C AND D IN UGANDA

BY

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The sickle-cell trait and sickle-cell anaemia, which have long been known, are associated with an abnormal shape of the red cell at reduced oxygen tensions. In 1949, Pauling *et al.* demonstrated that the potentiality for sickling is associated with a variety of haemoglobin which differs from the normal in its electrophoretic mobility.

This sickle-cell haemoglobin was at first called haemoglobin B (the normal being haemoglobin A), but it is now generally known as haemoglobin S. In the sickle-cell trait haemoglobin S usually forms from 25 to 45% of the total haemoglobin, and in sickle-cell anaemia from 85 to 100%. The former state is regarded as characterizing persons who are heterozygous for the sickle-cell gene, and the latter those who are homozygous (Neel, 1951).

Incidence

During the course of family studies of cases of haemolytic anaemia associated with sickling, Itano and Neel (1950) found a further abnormal haemoglobin, since designated haemoglobin C. This differs in electrophoretic mobility from both haemoglobins A and S. It is not associated with anaemia in the heterozygous C/A combination. The C/S combination, however, produces a haemolytic anaemia which is in many ways similar to sickle-cell anaemia though milder in degree (Kaplan *et al.*, 1953).

The incidence of haemoglobin C in the negro population of Detroit was estimated by Lawrence *et al.* (1952) to be about 0.3%; Smith and Conley (1953) found an incidence of 1.8% in 500 unselected negroes in Baltimore, while Edington and Lehmann (1954) found it to be as high as 12% in Gold Coast Africans. A further abnormal haemoglobin has been described by Itano (1953) which has the same mobility as haemoglobin S but differs in its solubility and in that it does not cause sickling. Like haemoglobin C this haemoglobin, now known as D, will cause a haemolytic

anaemia when in combination with S. Its incidence in American negroes is not known, but it must be much rarer than C. Apart from the studies of Edington and Lehmann on haemoglobin C in persons from the Gold Coast, haemoglobins C and D have so far been described only as occurring in American negroes. The combination of the single gene for sickling and the single gene for thalassaemia can also produce a haemolytic anaemia (Powell *et al.*, 1950). Thus, of all the cases of a haemolytic anaemia with sickling that are seen in America, most are true sickle-cell anaemia, but a proportion are due to the combination of the sickling gene with some other inherited abnormality of haemoglobin synthesis.

Thalassaemia, which is readily recognizable, is not known to occur in the Africans of tropical Africa, and hence it is unlikely that there are in Uganda any cases of anaemia due to the combination of the sickle-cell gene and the thalassaemia gene. It, however, appeared possible that some of the cases of apparent sickle-cell anaemia were due to the coexistence of haemoglobin S with C or D. In order to determine this, it seemed easiest to examine only non-sickling bloods—*in other words, to screen the population for possible haemoglobins C and D in combination with A rather than S and to preserve any of these bloods showing a double haemoglobin for identification elsewhere.*

Method

Bloods sent in to the laboratory for routine Khan tests were used. A sickling test was done, using a 24-hour *Bact. coli* culture and reading the unsealed preparation in two hours. All sicklers were discarded except one out of each batch, which was used as a control. As much serum as possible was drawn from the clot and discarded, and, after shaking, a drop of concentrated red cell suspension was withdrawn. To this was added a drop of 0.5% saponin in watery solution to cause lysis. Paper strip electrophoresis was performed in the Shandon apparatus with the apex height adjusted to 4½ in. (11.4 cm.) instead of the standard 7½ in. (19 cm.). A barbituric acid/sodium barbitone buffer of *p*H 8.6 and ionic strength 0.06 was used, and, with eight strips of Whatman No. 3, each 1½ in. (3.8 cm.) wide, electrophoresis was allowed to proceed at a voltage of 90–110, giving a current of 1.5–2 mA, for 12 to 18 hours. A sickling control was included in each run. The position of the haemoglobin could readily be seen without further staining provided the solutions were concentrated enough. If there was any doubt a washed and cleared preparation was made from the original clot and the procedure repeated.

Results

Of 500 bloods examined, 250 were male and 250 female. They were almost entirely adults. The tribal composition is not accurately known but is largely Bantu, of which the majority are Baganda. There were probably some 40 to 50 Nilotics. No case was found with a double haemoglobin, and all the haemoglobins migrated with the same speed as normal adult haemoglobin.

Conclusion

In a series of 500 non-sickling bloods examined in Kampala no example of haemoglobins C or D has been found. Since, on the other hand, there is known to be a considerable amount of haemoglobin C in West Africa, it is probable that this area is the source of the genes for haemoglobin C found in American negroes. This is, in any case, the most likely source, since the slaves largely came from this area. Most, if not all, of the haemolytic anaemias in Uganda, in which sickling appears to play a part, may therefore prove to be true cases of homozygosity for the sickling gene. There remains, however, the possibility that other modifying haemoglobins exist here which could be distinguished by properties other than electrophoretic mobility at alkaline *p*H.

I am indebted to the Director of Medical Services, Uganda, for permission to publish.

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Medical Memoranda

Death from Hexamethonium Ileus

In view of the increasing use of ganglion-blocking drugs in the treatment of patients with severe hypertension, this report of an avoidable death caused by one of these drugs may be of interest.

CASE RECORD

A carpenter, aged 54, was admitted to another hospital in April, 1953, in congestive cardiac failure, due to hypertension. He was discharged, improved by orthodox treatment, after three weeks.

In August, 1953, he was admitted to this hospital in a further attack of congestive cardiac failure with a blood pressure of 250/180 mm. Hg. He had now developed bilateral papilloedema with retinal haemorrhages and exudates. In view of the severe retinopathy it was decided to begin treatment with hexamethonium bromide in addition to full doses of digitalis and mersalyl.

On discharge, five weeks later, he was giving himself 200 mg. of hexamethonium subcutaneously three times daily. His blood pressure was fluctuating between 180/110 and 140/95 mm. Hg, whilst the papilloedema was beginning to regress.

At follow-up his dose was reduced to 200 mg. thrice daily, and he was advised to take 7½ mg. of neostigmine orally for his alimentary dysfunction. He took this dose for three days, when both eructation and diarrhoea ceased. However, on the fourth day he became obstructed and began to vomit, and on the fifth day he developed colicky abdominal pain. He continued to inject full doses of hexamethonium in spite of having been told to reduce the dosage if the diarrhoea or constipation should become severe. Only on the sixth day did he permit his wife to arrange for urgent readmission to hospital. He was found to be very dehydrated, with a thready, regular pulse and a blood pressure of 110/90 mm. Hg. The abdomen was greatly distended, particularly over the upper quadrants. There was some lower abdominal tenderness and guarding, and almost complete absence of bowel sounds. A radiograph of the abdomen showed gaseous distension of the small gut with fluid levels. Small amounts of gas and faeces were present as far as the hepatic flexure.

Ileus due to hexamethonium was provisionally diagnosed, and treatment was started with gastric suction and intravenous glucose-saline. A total of four pints of black fluid was aspirated from the stomach within the next four hours, during which time the patient's condition improved greatly. Further improvement seemed to justify continuation of conservative treatment, but 16 hours after admission the pulse rate rose to 120 a minute over the space of an hour, and his condition gravely deteriorated. Immediate operation was decided upon, as it was now thought likely that a perforation had taken place. The patient died before he could be got to the theatre.

Post-mortem examination within 3½ hours of death showed that operative intervention would have been valueless. The stomach and 5 to 6 ft. (1.5 to 1.8 metres) of small intestine were dilated and filled with foul faecal fluid. No perforation was found, but throughout the small intestine there were areas showing thinning of the bowel wall

with fibrinous reaction on the serosal surface. These areas ruptured on the slightest handling. The other findings were those expected in a case of malignant hypertension.

COMMENT

Bowel disturbances ranging from constipation with or without diarrhoea to complete ileus are not uncommon during the early stages of effective treatment with ganglion-blocking drugs. Most patients on treatment report occasional bouts of constipation, often accompanied by diarrhoea, though these attacks tend to become less frequent as time passes. During these episodes the urinary output falls. As hexamethonium compounds are not destroyed to any extent in the body, but are almost wholly excreted in the urine (Zaimis, 1950), oliguria leads to the building up of a dangerous concentration of the drug in the body, unless the dosage is cut down. This in turn can lead to further bowel atony, progressing to ileus, unless the situation is recognized and all drug treatment is withheld. This state of affairs may not be very obvious from clinical examination, as blood concentrations of the drug beyond a certain point do not necessarily produce a progressive fall of blood pressure. The ileus thus produced can lead to loss of bowel viability with consequent peritonitis.

In the ganglion-blocking drugs we have a powerful weapon which is life-saving in suitable cases. Their use does, however, require close and careful supervision. The patient should be warned to cut down or omit his injections when constipation becomes too obstinate, or when fever, vomiting, sweating, or diarrhoea threatens his urinary output. He should always consult his doctor when in doubt or in difficulties.

My thanks are due to Mr. P. F. Jones for sharing in the management of this case, and to Dr. R. A. J. Asher for permission to publish.

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Carbuncle of the Kidney

Perinephric abscess is not uncommon as a complication of a transient bacteriaemia, but a carbuncle of the kidney occurs only infrequently. Brady was able to review only 88 recorded cases up to 1932, and the condition is apt to be overlooked in considering the differential diagnosis of a possible perinephric abscess. For this reason the following case, in which the diagnosis was made with some certainty before operation, is presented in detail.

CASE HISTORY

A man aged 28 attended the out-patient department complaining of pain in the right loin and of anorexia, both of seven days' duration. The pain was continuous, of gradual onset, did not radiate, and was felt posteriorly below the last rib. There was no nausea or vomiting, micturition was entirely normal, and there were no symptoms referable to the other systems. He could remember no pustule or other possible septic focus in the previous two months.

The temperature was 100.2° F. (37.9° C.) and the pulse rate 86. In the right loin a smooth tender swelling was palpated bimanually, which moved slightly with respiration and appeared to be the lower pole of the kidney. There was no muscular rigidity, and no other abnormal physical signs were elicited. The urine was normal to chemical and microscopical examination. The patient was admitted and penicillin therapy was begun.

Investigations.—Urine: culture sterile after 24 hours. Blood: Hb, 75%; R.B.C., 4,000,000; W.B.C., 18,500 (polymorphs, 85%); urea, 34 mg. per 100 ml. *X*-ray report: "The outline of the upper two-thirds of the right kidney is normal, but the lower pole cannot be identified. The edge of the right psoas shadow is not seen. Slight lumbar scoliosis to the left. Normal left kidney and psoas shadows." Intravenous pyelogram: normal appearance of calices and pelvis on both sides. Cystoscopy: bladder normal in all respects. Retrograde pyelogram normal.

On these findings a confident diagnosis of carbuncle of the lower pole of the right kidney was made.

Operation.—The right kidney was exposed by the lumbar route on the second day after admission. There was oedema of the perinephric tissues, but no evidence of suppuration. The lower pole of the kidney was enlarged and fluctuant, but the surface appeared normal. A needle was inserted and thick yellow pus aspirated. The abscess was opened along the needle track, a finger swept round to break down any septa, and a drainage tube inserted around which the wound was closed. Some 5 fl. oz. (140 ml.) of pus was evacuated.

Culture of the pus secured at operation yielded a growth of *Staph. aureus* sensitive to penicillin. The temperature fell by lysis and was normal on the third post-operative day. Penicillin was discontinued the following day. The drainage tube was shortened on the 10th day and removed on the 13th. When the patient was discharged on the 20th day the wound was soundly healed and an intravenous pyelogram report stated: "Normal pelvis and calices, but the lower pole of the right kidney appears larger than normal. The psoas shadow is seen on both sides."

The patient has been seen at the follow-up clinic and has remained well.

COMMENT

The diagnosis of renal carbuncle is of importance in that, whereas observation of a perinephric abscess does relatively little harm, delay in treating a carbuncle damages more of an irreplaceable tissue at a time when the other kidney may also be infected. The demand for surgery is therefore urgent for two reasons—to drain the abscess in order to limit destruction of the kidney tissue and to secure pus for sensitivity tests.

The clinical features are admirably portrayed by this case, but whether the kidney is palpable depends first on the normal position of the kidney in the individual patient, and, secondly, on the site and size of the carbuncle. The degree of perinephritis determines movement on respiration. The findings in this case suggest that fixity occurs late, as this quite large carbuncle was still mobile on the ninth day of symptoms.

One would expect the outline of the enlarged kidney to show on an *x*-ray film of the abdomen, and Thomson-Walker (1948) gives this as a radiological sign of carbuncle, but in the above case it remained undefined until after operation, and clearly it and the psoas shadow were obscured by the perirenal oedema. A pyelogram may show the nearest calix to be deformed by the mass.

Fleming (1950) recommends treatment with penicillin only, but he stipulates that it must be continued for from three to four weeks and that a normal temperature and feeling of well-being are insufficient indications to stop treatment. He suggests that the drug may be stopped when the pyelogram returns to normal, but in the above case it was never abnormal. Even in this chemotherapeutic age the old adage, "Where there is pus, let it out," remains as true as when it was coined, for thereby toxaemia is relieved and resolution accelerated. Excessive fibrosis is known to occur as a result of delayed drainage of a pyogenic abscess treated with antibiotics (Stammers, 1953), and I have seen several breasts destroyed and a "frozen" hand from this cause. Antibiotics aid but do not replace the surgeon. If a carbuncle is suspected the kidney should be explored without undue delay, any abscess drained, and the pus submitted for sensitivity tests to indicate the most suitable antibiotic should one be required. Only rarely should nephrectomy, freely advocated in earlier writings, be necessary.

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Reviews

AMPUTATIONS

Amputations. By Leon Gillis, M.B.E., M.B., B.Ch., M.Ch.Orth., D.L.O., F.R.C.S. Foreword by Sir Harry Platt. (Pp. 423+xi; illustrated. 84s.) London: William Heinemann Ltd. 1954.

This is the first comprehensive book on amputations published in this country. It contains a great deal of information on all aspects of a small but not unimportant branch of surgery. It should be useful to those who treat traumatic conditions, to orthopaedic surgeons, and to those who fit prostheses; but it is not intended for the student who is required to learn the elements of the subject. The author's experience has been unique, and he has made full use of the teaching of those who started and developed the principles of modern amputation and the "service for amputees." The book is the outcome of years of work dealing with the amputees still alive from the First World War, with a large number of those from the last war, and an increasing number of civilians who have lost limbs.

It appears that Mr. Gillis realizes that this very specialized subject makes dull reading, and in order to induce surgeons to read the book and not merely use it as a work of reference he has illustrated it profusely and placed apt quotations, classical or modern, at the head of each chapter. The routine procedures and technique employed at Roehampton are described simply and clearly, and the index enables the reader to discover quickly what he wants, but he may have to refer to several chapters to get the information he requires.

The general instructions and information regarding the use of a tourniquet are helpful. The reader will find details of every type of amputation carried out to-day, and will be interested to find that Lisfranc, Hey, Chopart, and Pirogoff are still with us. There is particularly useful information on affections of and operations on stumps, on painful stumps, and on phantom limbs. The chapter on kineplastic procedures, including the Krukenberg operation, does not condemn them, but is written from only a limited personal experience. The management of children's amputations and prostheses is lucid and should be most helpful. The subject of amputation for vascular disease, including diabetes, is dealt with in rather too narrow a way to be of value.

This book has been written with authoritative knowledge and is to be followed by a sequel—*Artificial Limbs.* The production is of high standard which would not suffer from the exclusion of a number of illustrations.

ST. J. D. BUXTON.

SCIENTIFIC BIBLIOGRAPHY

Scientific Books, Libraries and Collectors: A Study of Bibliography and the Book Trade in Relation to Science. By John L. Thornton, A.L.A., and R. I. J. Tully, F.L.A. (Pp. 288+x. 24s.) London: The Library Association. 1954.

The authors succinctly sum up this book in their preface as follows: "The professional historian of science will find little new in these pages, but the student of the subject, and the scientist searching for 'bibliographical gaps,' will find between two covers an accumulated wealth of material on the bibliography of science." Even so, the scope of this book is too wide. In 12 chapters the authors have surveyed scientific literature before the invention of printing, scientific incunabula, scientific books from the sixteenth to the nineteenth century, the rise of scientific societies, the growth of scientific periodical literature, scientific bibliographies and bibliographers, private scientific libraries, scientific publishing and bookselling, and scientific libraries of to-day. With so extensive a field to cover, a book of this size had been better planned as an introduction to the subject of scientific bibliography, which could be read with profit by one embarking on the study for the first time. Instead, it is overweighted with erudition. It is too learned for the beginner, and, as the authors admit, is not adequate enough for the scientific historian, who will find many gaps in the chronology.

Some points of interest are the following: Dr. John Dee (p. 51) was an empiric, not "a medical man," as stated. He is believed to have had the degree of LL.D. of Cambridge University. Paracelsus (p. 53), so often regarded as a charlatan, receives his meed of recognition. The bibliographical study of Robert Boyle (pp. 71–4), based upon the writings of Geoffrey Keynes and John F. Fulton, is well done. Notable physicians in other branches of science were Claude Perrault (p. 83), who made contributions to comparative anatomy and then became a distinguished architect, and Martin Lister (p. 91), the founder of British conchology. Perrault's brother, Charles, achieved fame as a poet and a teller of fairy-tales. Scientific botany is the offspring of physicians, and Linnaeus had a medical degree. William Prout (pp. 142, 143) is mentioned as a British chemist. He was also a physician and a pioneer in biochemistry. So, too, was J. W. Thudichum, who is not mentioned, neither is E. B. Bancroft's *Philosophy of Permanent Colours.* Francis Buckland (p. 161) is cited, but not his father, Dean Buckland, so eminent as geologist and palaeontologist.

It is the duty of a reviewer to point out defects as well as merits. At the same time this book has many merits, much knowledge on every page, an excellent bibliography, and a full index. It should find a place in every large scientific and medical library.

ARTHUR S. MACNALTY.

TEXTBOOK OF ANATOMY

Anatomy: Regional and Applied. By R. J. Last, M.B., B.S., F.R.C.S. (Pp. 665+xii; 309 illustrations, many in colour. 55s.) London: J. and A. Churchill, Ltd. 1954.

During the last few years there have been several new books on human anatomy, and Professor Last's is the latest addition. It might be thought that there is no room for another book on anatomy, but this is not the case; there is always a place for a new book on this subject provided that it is a good one. And this is certainly the case with this book, for Professor Last has approached his subject from a new angle. He has placed emphasis on general principles to illustrate why structures are arranged in a definite manner. The practical and applied sides of anatomy have been stressed. Professor Last has the great advantage over the majority of anatomists in that he practised general surgery for over 20 years, and therefore is in a position to apply this practical background to his book.

It is certainly encouraging to find such a wealth of new and original illustrations in it, many of them from the author's own pen.

The arrangement of the volume, designed to meet the requirements of those reading for an examination in anatomy, is sensible and practical, for both the undergraduate and the postgraduate like to study the body region by region. The book can be read in the museum or in the quiet of the home, and the author intends it to be read with the appropriate bones and the prosected part or museum specimen at hand for constant reference. Miss Jessie Dobson has written a series of biographical notes on famous anatomists of the past—a very useful addition to a work which is bound to prove popular.

CECIL WAKELEY.

JUNG'S PSYCHOTHERAPY

The Practice of Psychotherapy: Essays on the Psychology of the Transference and Other Subjects. By C. G. Jung. Translated by R. F. C. Hull. (Pp. 377+xi; 14 illustrations. 30s.) London: Routledge and Kegan Paul. 1954.

Analytical Psychology is by no means a neatly systematized discipline resting on a few simple ideas and capable of application in treatment by means of a settled technique. This volume will be of special value to those who are interested in the clinical application of Jung's ideas, for particular attention is paid here to this aspect of his work. Part I

contains all of his papers on psychotherapy, and Part II his latest exposition of the transference situation. With one exception (the chapter on the principles of psychotherapy) the general papers have already appeared in English. Two of the papers were written in English by Professor Jung; the remainder have been excellently translated. Repetition is unavoidable in an assembly of eleven papers on therapy; but this is probably an advantage, as the reader will be able to see the development of Jung's ideas through the years.

Almost the whole of Part II is devoted to the only English translation of *Die Psychologie der Übertragung* ("The Psychology of the Transference"), which appeared as a separate publication in 1946; its inclusion here alongside the papers on psychotherapy is a sound plan and provides a fairly comprehensive picture of Jungian treatment. Analysis—as all agree—involves a reciprocal relation between patient and therapist, but this is hardly considered in some forms of psychotherapy, and in others it is given the central place. Jung's understanding of the transference makes it clear that the therapist is *in* the treatment and shares it with the patient.

Alchemical symbolism is extensively used in describing transference phenomena. This will strike some readers as rather odd, and they may wonder what link there can be between alchemy and present-day psychotherapy. They will find that Jung's study of alchemy is essentially practical and throws a clear light upon the transference situation in psychotherapy. Every psychiatrist using psychotherapy will find this chapter on transference worthy of his attention. The material does not make easy reading and it is not intended for the beginner. There is an excellent index and an impressive bibliography.

E. A. BENNET.

DUST HAZARDS

Dust is Dangerous. By C. N. Davies, D.Sc. Foreword by Sir George Barnett. (Pp. 116+xvii; illustrated. 21s.) London: Faber and Faber, Ltd. 1954.

In this book Dr. Davies has presented an outline of the medical and technical problems of dust diseases. He reviews the dust hazards of industrial workers, the methods and problems of dust assessment, and preventive measures. There are also chapters on radioactive dusts and on house and non-industrial dusts. These diverse and complicated problems are covered in 105 pages, so that the author has been forced to use a rather telegraphic style which often leads to some obscurity; but there are excellent illustrations and a good bibliography to lead the interested reader to sources of fuller information.

The book is presumably intended to awaken interest and to act as an introduction to the subject for those concerned with the practice of industrial hygiene but who have no expert knowledge of the subject. For them a glossary of technical terms would have been helpful, and perhaps a little more guidance as to the border-line between established practice and recent untried developments. Thus, illustrations are given of three dust-sampling devices which have not yet been accepted for general use, while the account of established instruments is rather cursory. In the clinical and pathological sections there are a number of minor errors and oversimplifications to which the medical reader may take objection, but on the whole the book is accurate and informative and should provide a useful stimulus to many people who do not realize how serious and complicated are the medical and technical problems of diseases caused by dust.

C. M. FLETCHER.

WARTIME PSYCHIATRY

Wartime Psychiatry: A Compendium of the International Literature. Edited by Nolan D. C. Lewis, M.D., and Bernice Engle, A.B., M.A. (Pp. 952. £6.) New York: Oxford University Press. 1954.

The editors claim that "the material in this book attempts a general survey of all the important psychiatric aspects of the problems of selection, administration, combat, demobilization, and rehabilitation of members of the armed forces. When possible, articles have also been included that bear on the application of new methods and knowledge to the field of civilian psychiatric practice."

In fact, no general survey, summary, or sifting of the vast literature has been attempted, for the volume consists of abstracts, varying in length, of individual books and papers. The selection of what should be included is in keeping with a most hospitable democracy. The abstracts are roughly grouped under 14 different general headings, sometimes for no very obvious reason. For example, the 17th abstract in the first section, "Administration," is:

"*Psychiatric Voice Recordings in the Military Service*
"(Albert A. Rosner, *War Med.*, **6**:38–41 (July) 1944)

"The author describes use of psychiatric voice recordings to supplement the printed word by the spoken word with its accompanying revelation of personality, feeling, character. The disks of one patient can later be cut as wished and transcribed to a single disk, but 10–20 per cent loss of clarity must be anticipated.

"The author presents 4 cases; case 1 is that of a psychotic soldier with dementia precox, paranoid type, which illustrates fantasy formation as a symptom."

The volume may possess some value as a work of reference, but the index refers only to the names of authors; it is therefore impossible to look up any subject or article unless the name of the author is known. Much labour by stenographers must have gone into this compilation. The printing is clear and the binding good.

DESMOND CURRAN.

HOSPITAL PLANNING

Hospital Planning Requirements. By Guy Aldis, A.R.I.B.A., A.A.Dipl. With a foreword by Professor H. W. C. Vines, James B. Ewen, M.D., D.P.H., and the late Lionel G. Pearson, F.R.I.B.A. (Pp. 257; illustrated. 85s.) London: Sir Isaac Pitman and Sons, Ltd. 1954.

The author in this excellent work displays considerable genius, including that part which consists in a capacity for taking infinite pains. His study of the complex problem of hospital planning shows much evidence of prolonged and careful inquiry and observation, constructive thought, and perfected description, both verbal and diagrammatic. Indeed, he deals with clinical departments and their ancillary departments so ably that it is to be hoped he will not delay long in presenting his suggested similar work on non-clinical hospital departments, such as the kitchens and engineering services.

Each section has a general pattern of text and numerous diagrams. The latter illustrate the functional circulation within the department under discussion and give examples of typical layouts, indicating clearly the author's preference. With so many diagrams the text can be commendably brief, but it contains a wealth of material; it gives explanatory notes and a schedule of the accommodation required in each department. This is therefore a book to be studied carefully, section by section, then retained as a reference-book for frequent use. It is not one to be borrowed for a single rapid reading. Whenever a new hospital department is being planned—and, just as important, whenever an existing department is to be adapted or extended—the team concerned (architect, doctor, nurse, and hospital administrator) will be well advised to digest the appropriate section of this book, and, having produced their plan, to re-examine it in detail against the functional circulation and the schedule of accommodation described by Mr. Aldis.

The production of the book is excellent, the print being good and the diagrams models of clarity. Mr. Aldis is to be congratulated on having made such good use of the opportunity for research on hospital planning afforded by his position as a Regional Architect in the National Health Service. His book fills an important gap in the literature of hospital planning and is worthy to be a standard text-book. A copy should be made available in the reference library of every hospital management committee and of all doctors and nurses closely associated with hospital planning.

W. G. PATTERSON.

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EXPERIMENTS ON HUMAN BEINGS

The question asked in Parliament last week whether an experiment on patients recently described in this *Journal* was ethical is but another example of a fairly widespread anxiety. At a meeting of medical editors in Rome last September, under the auspices of the World Medical Association, Dr. W. A. R. Thomson,[1] joint editor of the *Practitioner*, and Dr. G. C. Heringa, editor of the Netherlands journal *Medisch Contact*, read papers on the responsibility of editors in publishing the results of experiments on human beings, the nature of which might be abhorrent to the ethical conscience. The W.M.A. General Assembly passed a resolution on the ethics of human experimentation, and in his address to a large gathering of W.M.A. delegates the Pope lent the weight of his high authority to a series of pronouncements on this form of medical responsibility. The Pope recognized that Medicine could not do without human experiments: "Que la recherche et la pratique médicale ne puissent se passer de toute expérimentation sur l'homme vivant, on le comprend sans peine,"[2] to give his actual words. The conditions under which such experiments can be justified—are ethical—are not necessarily easy to determine. What to the doctor may be a seemingly harmless procedure may to the onlooker in Parliament or to the Press be something to be challenged in the name of ethics or morality. But doctors themselves have been the first to examine the ethical problems of human experimentation, feeling, perhaps, more than ever conscious of their responsibilities in this after learning of the black record of certain German doctors in the last war.

"Clinical investigators," W. B. Bean[3] has said, "rarely meditate upon the wide cleavage which separates clinician from investigator in their split personality." The physician caring for the sick person joins forces with him in the closest of all alliances against a common enemy—the affliction that has laid the patient low. In the face of an intractable disease for which there is no specific remedy the physician—and still more the surgeon—may offer the patient a drastic remedy which may fail to do good or may do actual harm. Each such intervention by the doctor is an experiment. The first appendicectomy was an experiment, as were the first lobectomy, the first removal of a cerebral tumour, the first administration of penicillin. Both patient and physician in the face of disease or disablement feel a strong urge to intervene actively, and in the days when therapeutics was only barely rational the bleeding bowl, the cupping instruments, and the enema syringe were always at hand for use and misuse A mediaeval physician proposing to put bleeding to a controlled trial in the treatment of a given disease would have been looked on as beyond the pale. But a simple trial might have saved thousands from being bled to death. The modern clinician must be clear in his own mind what he is doing when taking part in a trial of a new drug in treatment or a new vaccine in prevention of infection, both presumed to have the possibility of being effective or they would not be on trial. If a large-scale trial of, say, pertussis vaccine or a poliomyelitis vaccine is undertaken, with comparable groups of children serving as controls to those receiving the prophylactic, in what scale of ethics is one to weigh the increased morbidity and mortality subsequently found in the control group—a large enough difference being found to justify widespread inoculation of later generations of children against these diseases? Of course every safeguard is introduced. Parents and schoolteachers are informed with the greatest scrupulousness of the nature of the experiment, of its object, of the risks entailed; and the investigation is then conducted on a voluntary basis. But however careful and conscientious the explanation—unfortunately often described as propaganda—there is a limit to the layman's understanding of it. Probably what finally tips the balance in most cases is trust and faith in the doctor, in the wonders of modern medicine. Yet without such controlled trials it is difficult, if not impossible, to prove the prophylactic value of a vaccine or the superiority of a new variant over an old one. The history of B.C.G. shows what confusion may prevail for more than a quarter of a century in the absence of proof—the proof that only an experiment can provide. In therapeutic trials it is interesting to note that only strict limitation of supplies of the drug made it possible for controlled trials of streptomycin in the treatment of tuberculosis to be conducted in this country: in this instance necessity was the mother of ethics; indeed, it would have been unethical not to have controlled the trial that was made. No one can doubt the great benefit conferred on tuberculous persons the world over as a result. Much heartaching

[1] *Med. J. Aust.*, 1954, **2**, 953.
[2] *L'Osservatore Romano*, October 2, 1954.
[3] *J. Lab. clin. Med.*, 1952, **39**, 3.
[4] *Science*, 1953, **117**, 205.

disappointment would be avoided if no new drug were made generally available except after previous carefully conducted clinical trials, except after, in other words, the essential test of human experimentation. The story of cortisone is a warning.

The stronger the influence of the laboratory in Medicine, the more tempting it is for the investigator to look upon his patients or the patients of his colleagues as "experimental material," as cases of this, that, or the other disorder, rather than as sick and anxious human beings longing to be relieved of distress of mind and body. To some extent such detachment of viewpoint is essential if the doctor is to do his best for the patient, by looking on him with complete objectivity. But modern instruments and techniques make it easy for the medical man to satisfy his scientific curiosity by subjecting patients to procedures not essential to the relief of the condition for which they are being investigated or treated. When these procedures are simple and free from risk, then surely there is everything to be said for them when knowledge is added to. The main requirement is full explanation to patient or parent before permission is obtained. And some would distinguish sharply between experiments on the sick and experiments on the healthy. In the former an experiment may lessen the consequences of disease. A doctor voluntarily contracting a tropical disease to discover some link in the chain of causation is one thing; to subject a lay person—even a volunteer—to a similar experience is another, especially if the lay person is in a subordinate position.

What safeguards should the medical profession erect to protect the public and to preserve its traditional *mores*? The first, and the oldest, and the most obvious imperative lies in the nature of the doctor's first task—to care for the sick person, the man or woman in pain or distress, to submit himself to the rigorous demands of the doctor–patient relationship, to do nothing to his patient that he would not do or have done to his own family. Mr. B. Shimkin[4] considers that the clearest rules for guidance were those laid down at the Nuremberg trials. The first of these is here given in full:

"The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

"The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity."

Some hold that editors of scientific journals have a prime responsibility in this matter in being able to reject articles recording the results of allegedly unethical experiments. But it might be argued that an editor should publish papers which contribute to knowledge and should not act as a censor of morals. It might with more force be argued that it is only by publication that undesirable methods of investigation are brought to light and exposed to public criticism. Whatever may turn out to be the best methods of discouraging and preventing undesirable experiments on human beings, it is heartening to note that medical men all over the world are alert to the dangers; and it is deeply satisfying to record that human experimentation has contributed immeasurably to the health and well-being of countless millions. The continued progress of Medicine will depend upon its continued use under wise and humane guidance.

ADRENAL CORTEX

The review by Dr. R. I. S. Bayliss of recent advances in our knowledge of adrenocortical function, which appears in our opening pages this week, may be welcome to those many medical men who are apt to be somewhat daunted by the intricate chemistry and terminology of the subject. The adrenal cortex secretes five groups of substances, all of which are related in chemical structure to cholesterol. This sterol is widely distributed throughout the body, and from it all the adrenocortical hormones, regardless of their function, are thought to be derived. Two groups of hormones have been most widely investigated, chiefly because their absence is most dramatically marked by the inability of the deprived animal to go on living. These are, first, the hormones whose primary effects are on carbohydrate, nitrogen, and fat metabolism, and, secondly, the most recently isolated steroid aldosterone; this exerts its most powerful effect on sodium, potassium, and water metabolism. The functional distinction between the two is not clear-cut, since the steroids concerned with carbohydrates, commonly known as corticosteroids, exert some effect on sodium, potassium, and water conservation, while aldosterone to some extent corrects the tendency to hypoglycaemia from which patients with decreased or

absent adrenocortical function suffer. So far little is known of how aldosterone is secreted, or of how it produces its effects, and most research has been concerned with the secretion of the carbohydrate-active compounds, of which cortisone and hydrocortisone are important examples.

The secretory activity of the adrenal cortex is under the control of the corticotrophic hormone (A.C.T.H.) of the pituitary. This substance is not itself a steroid, but is either a protein or a polypeptide, and there is some disagreement whether it is one hormone or several. It exerts its effect on the adrenal cortex by causing increased synthesis of cortical hormones from cholesterol and acetate, the intermediate chemical keystone of the whole process probably being the hormone progesterone. Since there are at present no reliable methods by which the A.C.T.H. concentration in body fluids may be estimated, little is known about the levels which are necessary to ensure adequate adrenocortical secretion for coping with the vicissitudes of everyday healthy life. When A.C.T.H. is not secreted because of hypopituitarism, the suprarenals atrophy and secretion of corticoids is minimal. When a patient is given A.C.T.H., corticoid secretion increases, as shown by increased corticoid levels in the blood, by increased excretion of corticoids in the urine, and by the effects of the corticoids themselves on the level of circulating eosinophils, lymphocytes, and blood-sugar concentrations. The amount of stimulus exerted by administered A.C.T.H. depends on the dose of A.C.T.H. given and on the time over which a constant dosage can be maintained without intermission. A single dose of A.C.T.H., which must be given parenterally, produces a transient enhancement of adrenocortical secretion; laboratory evidence of this may be missed in the commonly used Thorn test of adrenocortical function. Therefore negative results to this test, as usually done, should be confirmed by a stimulus of longer duration. This can be provided by intramuscular injection of A.C.T.H. mixed in a gel, or preferably by intravenous infusion.

The level of corticosteroids in the blood probably controls the release of A.C.T.H., while corticosteroids are secreted into the blood in response to stimulation of the adrenal cortex by A.C.T.H. In healthy subjects the mean plasma corticosteroid concentration averages 9 μg. per 100 ml., ranging from 3 to 17 μg. per 100 ml. The method estimates chiefly hydrocortisone (compound F). Its value as a method of assessing adrenocortical function is limited by the same considerations which apply to all estimations of blood concentrations—namely, that the blood level of any substance is a resultant of the rate at which the substance is discharged into the blood and the rate at which it is removed by metabolism or excretion. Corticosteroids are excreted in the urine and probably in the faeces. They may be estimated in urine, in which they are excreted partly metabolized to 17-ketosteroids and other steroids and partly unchanged as water-soluble conjugates with glucuronic and sulphuric acids. Unfortunately there are not yet any satisfactory routine methods for determining specific corticosteroids in the urine. This is because of the difficulty of hydrolysing the conjugated excretion product without altering the chemical structure of the hormone beyond recognition. It is known that 5–10% of an administered dose of cortisone is excreted in the urine as cortisone, and a very small amount appears as 17-ketosteroids. The fate of corticosteroids in the tissues is obscure. They diffuse freely throughout the extracellular fluid and are metabolized by synovial tissue, kidney, spleen, and liver. In the liver they may undergo chemical reduction and conjugation with acid radicles, and are partly excreted in the bile. The renal clearance of corticosteroids is low, and they are probably actively reabsorbed in the renal tubules.

While the pathogenesis of Addison's disease and hypopituitarism are obvious enough, it is clear that in such a complex system there is plenty of room for disorders of steroid production, consumption, and excretion, and these may be reflected in clinical syndromes whose aetiology is at present only dimly understood, if at all. Much remains to be done in this field of research.

ENDOCRINES IN PSYCHIATRY

A lucid and compendious account of endocrine treatment in psychiatry is given by Dr. R. E. Hemphill at p. 501 of the *Journal* this week. The story is, admittedly, a somewhat disappointing one. Almost everywhere in psychiatry the endocrine balance seems to play some part—in the psychoses, in many forms of neurotic reaction, and in personality and constitution; and yet the points at which the endocrinologist can effectively enter into treatment are few and far between. Dr. Hemphill has himself drawn attention to some of the reasons why this is so; there are also others. However, things are not quite so bad as they seem at first. When some form of psychiatric disorder proves to have a physical cause, diagnosis and treatment are taken from the hands of the psychiatrist and reserved for the physician. It is not so long since dysmenorrhoea was regarded mainly as a neurotic disturbance; either no treatment was given or it was a case for psychotherapy. More is now known about the physical basis—for instance, that the pain may be

related to ovulation. If ovulation is suppressed, as it may be by giving oestrogen early in the menstrual cycle, the pain may disappear. Superficially the cycle appears to be the same, though its hormonal balance is now different. The treatment, which might once have been regarded as a successful application of endocrinology to psychiatry, would not now be thought of as having anything to do with psychiatry at all. The same position has been reached with the premenstrual tension state, and, to a large extent, with the emotional instabilities of the menopause. Such endocrine disorders as Graves's disease, myxoedema, Addison's disease, and Cushing's disease, despite their important psychiatric aspects, rarely come the way of the psychiatrist and are treated with some success by physicians without recourse to the psychiatrist. This has the disadvantage that the psychiatrist never sees this kind of clinical material, though it would be of great educational value to him. The cases that the endocrinologist refers to the psychiatrist, like the cases passing in the opposite direction, are those with atypical features, in which on each side the clinician feels at a loss. Here are the unsolved problems involving both specialties, which neither side can tackle alone.

Early studies of glandular disorders gave an altogether false impression of their aetiology, suggesting that every such illness should fall into the simple pattern of diabetes, in which the replacement of a single hormone is effective treatment. In the endocrinopathies this is a most unusual state of affairs. Generally it is the balance of a number of internal secretions which is at fault, and there is no simple replacement that can be carried out. In treating the premenstrual tension state, for example, administration of ethisterone in the latter half of the cycle is only moderately successful, and sometimes does not avail. At this time the oestrogen level is at its maximum, and the progesterone level should be rising to compensate for it. The imbalance may arise through deficient corpus luteum formation and inadequate absorption of progesterone ; in that case the administration of a progesterone compound may give benefit. But the imbalance may also arise through an excessive production of oestrogen ; then the giving of oestrogen in the first half of the cycle, influencing the production of follicle-stimulating hormone (F.S.H.) by the pituitary and suppressing the formation of a corpus luteum, will so alter the cycle as a whole that the same therapeutic end is attained by what would seem to be physiologically contrary means.

The administration of a single endocrine preparation often fails to restore normal balance ; furthermore, it cannot be given without repercussions. Supplying an extra amount of one internal secretion not only alters the level of that one compound but also affects the level of many others, and the prolonged administration of any one endocrine substance will probably depress the function of the gland that makes it. While no general rule can be formulated, it is safer when the pathology is not clearly understood to give balanced complexes rather than single gland products, and to give treatment intermittently—in short courses with rests between. There are yet other dangers of inexpert treatment, many still not fully known. It seems rather doubtful whether there is such a condition as a male climacteric—that is, a revolution rather than an evolution of hormonal balance—but the diagnosis is sometimes made, and hormones are sometimes given for it. But the risk is by no means negligible that the administration of androgens may start up a prostatic carcinoma. Even when the nature of the disease is known and the treatment is uncontroversial, caution is often necessary. Deaths from myxoedema have been reported (for example, in cases in which adrenal function was depressed) caused by the administration of thyroid extract in a dose too high for the patient, though moderate by ordinary standards.

The future of endocrine treatment in psychiatry is encouraging enough. More research is still needed, though not crude experiments matching degrees of mental improvement in treated and control series of patients whose hormonal balance is entirely unknown, for these can give only misleading results. And it is to be hoped that official bodies responsible for the distribution of scarce preparations, such as cortisone, will be more sensitive to psychiatric claims.

NUMBERS OF DOCTORS

The news that a Government committee has been set up to consider the intake of students into the medical schools is welcome. As reported in our Parliamentary news (p. 546), the Minister of Health and the Secretary of State for Scotland have appointed Mr. Henry Willink, Q.C., as chairman ; the ten other members of the committee comprise seven medical men and three laymen. Their combined experience of medical affairs, both clinical and administrative, will provide a firm foundation for their debates. Not quite so much can be said for their terms of reference. They read as follows:

> "To estimate, on a long-term basis and with due regard to all relevant considerations, the number of medical practitioners likely to be engaged in all branches of the profession in the future, and the consequential intake of medical students required."

Though the total number of doctors practising at some future time may be estimated fairly accurately, provided

certain common-sense assumptions are made, the distribution of those doctors between the branches of the profession may well change unexpectedly in response to the development of medical science and its clinical applications. No good purpose is served by trying to work out, on the basis of the existing distribution, the numbers required to fill complex hierarchies in the hospital or public health branches. Moreover, the distribution between even the main branches of the profession has changed, and continues to change, in accordance with the needs of efficient medical practice. Flexibility of response is apt to be lost sight of in a State service, and it is to be hoped the committee will so interpret their terms of reference as not to impair it. The ambiguity in these instructions about what the size of intake is to be a consequence of, and what requirements it ought to meet, is presumably intentional. No doubt the committee will treat them as a starting-point rather than a boundary.

It was two years ago that the Council of the B.M.A. accepted a suggestion made by the chairman of the General Medical Services Committee that the G.M.S. Committee should look into these questions of supply and demand, and last year the Council asked the Minister "to set up a working party to review the whole problem."[1] Since then nothing has happened to make it any less urgent. As we pointed out last year,[2] there were in 1953 about 900 persons in England and Wales to one doctor and rather under 600 in Scotland. These figures, still the latest obtainable, are derived from the numbers of doctors shown in the *Medical Directory* as living in these countries. Some may be retired, and others who are practising do not have their names listed, but these are only trivial sources of error. The corresponding figure for Ireland is 730 persons per doctor, though, since Northern Ireland and the Republic are not treated separately, the figures are difficult to interpret. In 1900 England and Wales had 1,410 persons to every doctor and Scotland 1,300. From about 1930, when England and Wales had 1,250 persons per doctor, the proportion steadily fell to the 1953 figure of 900. In Scotland as far back as 1920 there were only about 1,000 persons to every doctor; during the 'thirties there were about 800, in 1953 there were about 570. Meanwhile students have been pressing at the gates for admission to medical schools in considerably greater numbers than are finally admitted, and as a result of their exertions the average annual increase of names on the *Medical Register* has been more than 1,000 for at least the last 20 years. In 1934 there were 57,496 names, in 1953, 83,090; this is an increase of 25,594, or 45%. Evidently, therefore, one of the most "relevant considerations" before the new committee will be the swiftly growing body of registered medical practitioners, for when the present new intake emerge from the chrysalis in 1960 their names will be added to a *Register* whose list will then have increased by five or six thousand. The committee may well feel some urgency about its work.

[1] *British Medical Journal Supplement*, March 27, 1954, p. 86.
[2] *British Medical Journal*, 1954, **2**, 53.

TOPICAL HYDROCORTISONE

Cortisone and corticotrophin have been available for long enough now to give a fairly clear impression of their value in the treatment of skin diseases. They are used in two principal types of case: the severe but self-limiting disorder in which steroids will cut short an attack and tide the patient over until natural remission sets in; and those long-term cases which are otherwise fatal or severely disabling and for which no alternative treatment gives much benefit. In the former type of case the patient is often treated for only a few days at a time, and the well-known complications of treatment with these substances scarcely have time to develop. But when treatment is prolonged over many weeks and months a formidable list of complications may appear, some of them wellnigh unavoidable. It is therefore of particular interest to determine what benefit may be expected from the local application of steroids.

It was early discovered that cortisone and A.C.T.H. are almost, if not completely, without effect when applied to the surface of the skin, but that hydrocortisone (compound F) exerts a profound influence on certain eruptions. It is evidently absorbed through the skin, particularly if the corneous layer of the skin is damaged by disease; but the experiments of C. C. Smith[1] failed to demonstrate any eosinophil response to the application of relatively large amounts to the intact skin surface. Similarly, the application of hydrocortisone to the skin over periods of many weeks is not followed by any signs of systemic absorption. The precise mechanism and level of action of topical hydrocortisone therefore remain unknown.

Although the therapeutic effects of systemic cortisone and local hydrocortisone are not quite the same, they correspond fairly closely, and in many disorders local application is preferable in that the risk of the complications and side-effects of its systemic administration is avoided. Moreover, local application of hydrocortisone appears to be surprisingly free from irritation. In all those cases where irritant action has been recorded, it appears to have been due to the base, usually carbowax, in which it was incorporated; true epidermal sensitivity to hydrocortisone has not been demonstrated. Dr. R. Church, whose results are reported on another page, used a base of lanolin, soft paraffin, and mineral oil, and does not record any irritation from this.

M. B. Sulzburger[2] has listed those disorders in which hydrocortisone appears to be beneficial. Most belong to the eczema group, whether of the so-called constitutional type or the type of case due to contact sensitivity. Atopic eczema, both the infantile and the flexural, otitis externa, and pruritus ani are also likely to respond. Dr. Church confines his account mainly to those disorders which have already been shown to improve with this kind of treatment, and his results, successful in about three-quarters of the cases, are comparable to those of other authors. It is notable that most of these diseases

[1] Smith, C. C., *Arch. Derm. Syph. (Chicago)*, 1953, **68**, 50.
[2] Sulzburger, M. B., in *Modern Trends in Dermatology*, 2nd series, Editor, R. M. B. MacKenna, 1954, London.
[3] —— and Baer, R. L., Editors, *Year Book of Dermatology*, 1953-4, Chicago.

are of unknown, or only partly understood, causation, and that they run an unpredictable course with spontaneous exacerbations and remissions. To measure the benefit conferred by any new treatment is thus a matter of the greatest difficulty, and the final assessment of hydrocortisone ointment will not be made for some years. However, even when allowance is made for natural optimism, it seems likely that M. B. Sulzburger and R. L. Baer[3] will be proved right when they surmise that it bids fair to being one of the most important advances ever made in local treatment of the skin. The disorders which will or will not respond to hydrocortisone ointment are now fairly clearly defined. Suitable vehicles and bases in which to incorporate the active substance have yet to be decided, as have the mode and frequency of application required in different cases. The combination of hydrocortisone with antibiotics and other drugs has already been considered, but so far hardly studied; combinations of local treatment with systemic steroid therapy also need investigation.

TREATMENT OF BACTERIAL ENDOCARDITIS

Since the conclusion of the Medical Research Council study of the penicillin treatment of subacute bacterial endocarditis, the findings of which were reported by Cates and Christie,[4] it has been left to individual effort to pursue this subject. Possibly the lessons learned in that study are still being applied, but there is almost no means of knowing how successful their application is proving, or whether any improvement in the method of treatment has had an adequate trial. It would be interesting in particular to know whether, and if so in what circumstances, the disease can safely be treated by less frequent injections of a slowly absorbed penicillin preparation, a modification which would be welcomed by patients who have to endure a course lasting six weeks. The results obtained with procaine penicillin by Roston and Stollerman[5] in six patients, and by Volini, Hoffman, and Hughes[6] in sixteen appear to have been very satisfactory and fully warrant more extended trial.

Not only the method of treatment but the grounds of the decision to institute it are matters of importance, and on the second of these subjects Newman, Torres, and Guck[7] have decided and somewhat controversial views. Their material consisted of 52 cases, all men, admitted to the Veterans' Administration Hospital, Bronx, N.Y., between 1946 and 1953. Only 12 of these were diagnosed before admission, and apparently 8 died undiagnosed. Blood cultures were made in 48, of which only 32 were positive: in "some" cases daily cultures were made for 15 to 20 days, and in none was a positive culture obtained after the fourth when the first four had been negative. On this basis these authors propose the following policy. It depends on the presence or absence of signs of the disease, classified as "major" (these, apart from a positive blood culture, are heart murmur, fever, and anaemia), and "minor" (palpable spleen, petechiae, clubbing, microscopical haematuria, arterial emboli, and Osler's nodes). If a patient with a cardiac or vascular lesion predisposing to infection has one or more of these signs inexplicable in another way, he should have four blood cultures on successive days and then be submitted to a full course of treatment without awaiting the results of these cultures. The authors say earlier that if a murmur associated with one other major or two minor signs had been accepted as diagnostic, 47 of their cases could have been diagnosed. This policy is well expressed in their dictum: "We must have a very high index of suspicion for this disease even if it means treating some patients unnecessarily."

This series of patients is not altogether satisfactory for several reasons: at least three and possibly five were infected by organisms which place them outside the category of a "subacute" endocarditis, no sensitivity tests were reported, and treatment in some of the early cases was inadequate. Even "adequate" treatment is defined as a certain dose given for "at least two weeks," which in most people's estimation is much too short a period. Nevertheless, some other conclusions, even though based on small numbers, are interesting. Of 39 adequately treated patients 27 recovered, of whom one-third each died of sequelae, are alive but disabled, and alive and symptom-free. The duration of the disease, if not exceeding six months, did not appear to affect the amenability of the infection to treatment, nor did the presence of congestive heart failure, which actually preceded the onset of the infection in five patients, and was the first sign of it in eight. On the other hand, the mortality in such patients is much higher. Positive blood cultures were obtained in three afebrile patients. Provided the infection could be cured, recovery from renal damage was possible. Previous inadequate antibiotic therapy did not affect either the chances of obtaining a positive blood culture or the outcome of subsequent treatment. Two of the more heterodox of these conclusions—namely, that neither the duration of the disease nor the existence of heart failure appears to affect the results of treatment—are also reached by Bunn and Cook[8] from a study of 48 patients, of whom 33 recovered. These authors are insistent that the dose of penicillin must be adjusted to the sensitivity of the infecting organism. Inadequate dosage was a probable cause of failure in 4 of their patients; in 6 others rupture or perforation of an aortic valve cusp was the immediate cause of death. It is emphasized that the outlook when the lesion is aortic is far less favourable than in involvement of the mitral valve or of congenital defects. Analyses such as these, even though some of the conclusions rest on a slender basis, provide helpful information, and those in a position to report on such a series should be encouraged to do so, particularly if it illustrates the effects of any newer method of treatment.

[4] *Quart. J. Med.*, 1951, **20**, 93.
[5] *Amer. Practit. (Philad.)*, 1949, **4**, 102.
[6] *Cuore e Circol.*, 1949, **33**, 12.
[7] *Amer. J. Med.*, 1954, **16**, 535.
[8] *Ann. intern. Med.*, 1954, **41**, 487.

We record with regret the death on February 21 of Sir Henry Wade, the eminent urological surgeon, who was on the staff of the Edinburgh Royal Infirmary for nearly thirty years before his retirement in 1939.

EMERGENCIES IN GENERAL PRACTICE

"FITS"

BY

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By the time he gets to the house the doctor will find that the fit itself is over and that the patient is either recovering or is in post-epileptic coma or in a restless confused state. It is best then to do as little as possible, for restraint or restriction will cause an increase in restlessness or aggression; the sleeping patient is best undisturbed.

If this is the first fit the question to be answered is whether it was an epileptic convulsion, an hysterical attack, apoplexy, a subarachnoid haemorrhage, or even an unsuspected head injury with subsequent coma. A witness's account will usually establish the characteristic train of events in a convulsion—sudden tonic spasm occurring without cause, followed by gradually decreasing clonus with tongue-biting and cyanosis, and then coma with flaccidity, incontinence, and stertorous breathing. If there is doubt about the nature of the attack, it is best not to hurry into action because time and the recovery of the patient will in most circumstances make the diagnosis clear. He will recover from post-epileptic coma in a few minutes or a few hours with no sequel other than a headache, a badly bitten tongue, and incidental soreness and bruising. The family will probably need more treatment than the patient, and the advice given should be very conservative. It is best to tell relatives that a fit itself does the patient little harm, barring accidents, that it is an explosive affair affecting the whole body, and that like any other explosion there is nothing that can be done until it is over. Then the thing to do is to repair the damage and try to prevent a recurrence.

When a patient falls in a fit he should be left where he lies, furniture and obstructions being removed from the area of movement to prevent injury. There is no need to loosen clothes or to try to modify his activity in any way. In the early tonic phase the mouth opens and there is plenty of time to remove dentures and to rest something against the upper premolar teeth to prevent subsequent tongue damage; a bit of stick or a screw of stuff will do, or the patient's diary, a pencil, a handkerchief, or the corner of his coat collar. Once the clonic phase is over the patient can be laid somewhere comfortable and allowed to recover without interruption. At this stage a brief examination of the nervous system may show weakness of one limb after the others have recovered, or a unilateral extensor plantar response, which may provide a valuable clue concerning the cause, which will completely disappear and be lost in a few minutes.

After recovery from the fit—perhaps the next day—the reasons for the attack must be considered. There are immediate precipitants and remote causes. The more potent the immediate causes, the less serious are the remote ones likely to be. A normal person may have a solitary fit after excessive beer-drinking, through sheer hydration, and some will complicate pneumonia with a convulsion. Others will have a solitary fit during a period of prolonged emotional and physical strain. When immediate causes have been considered, the more remote ones will be looked for—sugar or albumin in the urine, raised blood pressure, an enlarged liver, or a history of recent ill-health will suggest a host of general medical conditions which may give rise to convulsions. The local cerebral causes, revealed by signs of local dysfunction or the symptoms of raised intracranial pressure, will then be excluded. Every adult who has had a solitary fit without known cause should be fully examined by the physician, have his urine tested, and then be referred for an electroencephalogram, radiology of the chest, blood Wassermann reaction, and radiology of the skull in that order of importance.

No person who has had one solitary convulsion should be given anticonvulsants—he may never have another fit. Unless there are special circumstances, it is more reasonable to allow a period of time to elapse, to withhold treatment until investigations have been completed, and, other diseases having been excluded, to begin treatment if two more fits occur. Three attacks may give some indication of the natural periodicity without treatment, which will help in the assessment and consequent management of the case.

A Convulsion in a Child

A convulsion occurring in childhood has much less serious significance than in later life, as regards both prognosis and causation; for the younger the infant, the more readily do transient bodily changes induce a fit. There is no difference between a teething convulsion and any other sort of fit; it is simply that the tendency to convulsions with similar causes is progressively diminished with maturation of the nervous system. As in the adult, the more closely the convulsion can be related to an immediate cause, the less intensive need be the search for remote causes; in infancy, pertussis, pneumonia, measles, chicken-pox, or teething, in that order of frequency, may be the whole and sole cause of a convulsion. Do not treat these symptomatic convulsions, but begin to consider the matter to be serious if a fit is repeated more than once, whatever the cause; if there are several convulsions in one illness; or if there is a single fit without an adequate recognized cause. If any of these circumstances obtain, the time has probably come to begin anticonvulsant therapy.

Focal Attacks

So far generalized convulsions only have been mentioned, but the same management may be adopted for the focal epileptic attack. Here, however, the immediate event is less dramatic and exacting, but a searching investigation of the patient for evidences of a local cause should be made. At this stage the physician will generally find negative results of his initial investigations, and it is rather worrying to know how far to pursue them. As neurological investigations carried out in hospital, including as they do carotid arteriography and air encephalography, are both complex and distressing, it is often wise merely to re-examine the patient and to have an electroencephalogram done at infrequent intervals—perhaps every other month.

Status Epilepticus

Status epilepticus is the most deadly complication of epilepsy and sometimes is the first event in the illness. It is said to occur when a patient has more than two fits without recovering consciousness, and at that stage it must be treated as a grave emergency. It is too late to save his life if you wait until the patient begins to look as if he may die, because death usually occurs through acute myocardiac failure, which rapidly progresses if fits continue after its onset. Consequently a patient in status epilepticus, if possible, should be sent to hospital after initial treatment. Intramuscular sodium phenobarbitone, 5 gr. (0.32 g.), is most often given first, but an intramuscular injection of sterile paraldehyde, 5 or 10 ml., repeated in an hour if the fits continue, is more effective. It is best to err in giving

a large rather than a small amount. If the patient is in a hospital where an anaesthetic apparatus for positive-pressure respiration is available, intravenous thiopentone or amylobarbitone sodium, both given very slowly until the movements stop, are highly effective. The injection should cease when clonic movements cease, to be repeated later if necessary, for, as the patient is already in deep coma, it is impossible to judge the depth of anaesthetic coma, and respiratory and cardiac action may cease. It used to be said that a half of all patients in status epilepticus die, but death should now be thought to be due to delay in instituting parenteral treatment.

When the actual clonic movements of the limbs of a patient who is in status epilepticus cease, post-epileptic coma may continue for many hours, and confusion for days, but if the patient's general condition is good there is now no need for immediate concern. During the coma any feeding should be by a Ryle tube, in small amounts, to prevent the possibility of aspiration pneumonia. Intravenous infusion of glucose–saline should not be needed, and in any case fluids should be given sparingly, as hydration of the patient may well precipitate further fits. Sometimes after freedom from convulsions for some hours they will repeatedly recur; then it is wise to put up a slow intravenous saline drip with thiopentone and to inject into the tube from time to time, but in those circumstances a whole team made up of physician, anaesthetist, and nurses is needed. A patient should remain in bed several days after status epilepticus has been controlled, even if there are no complications, both for recovery and for repeated examination.

Recurrent Fits

When more than two fits have happened, and investigation has failed to show a cause requiring specific treatment, continued anticonvulsant treatment will be needed, but before beginning this the physician should face the fact that he is implying that medical treatment must continue for at least three years after the last attack. This is a consequently serious step requiring much consideration; I think some doctors are far too apt to "put him on phenobarb." to ease domestic tension as much as anything else, when it would be more logical, effective, and economical to give the relatives phenobarbitone for a few days instead.

Although this paper is dealing with emergencies, it is logical to consider the treatment of repeated convulsions. For the major fit phenobarbitone remains the anticonvulsant of choice—it is so often effective, and its side-effects are usually so trivial. I generally begin in an adult with ½ gr. (32 mg.) twice a day, increasing to thrice a day if necessary. Children tolerate phenobarbitone well, and as a rule they are given too small a dose in attempting to control convulsions; a suitable dose is ¼ to ½ gr. (16 to 32 mg.) twice a day. The timing of the dose should depend on the usual time of occurrence of the fits—a large dose in the evening if they are mainly nocturnal, but on rising if they are diurnal. Similarly, menstrual or pre-menstrual convulsions can be treated with much larger doses in the week before the period than at other times.

The hydantoins (tab. phenytoin sod., 1½ gr.—0.1 g.), in a variety of proprietary forms, should next be used, preferably with phenobarbitone, and they may be combined in a ratio of phenytoin 2 to phenobarbitone 1 in the same capsule. If toxic effects arise with one of the hydantoins, two different kinds may be given together in smaller doses to obviate them. If fits are not controlled, I then use primidone up to four or five tablets in the day, mainly because this substance is particularly effective for pure major convulsions without evidence of organic brain disease. Since focal attacks and petit mal cannot be regarded as emergencies, I may be excused from including their treatment in this short review.

Next article on Emergencies in General Practice.—"Attempted Suicide," by Dr. I. R. C. Batchelor.

EDUCATING THE PUBLIC IN MENTAL HEALTH

The education of the general public in mental health was the theme of discussion at the final session of the quarterly meeting of the Royal Medico-Psychological Association held in London on February 17. Dr. NOEL G. HARRIS, the president of the association, was in the chair.

Miss P. HORNSBY-SMITH, M.P., Parliamentary Secretary to the Ministry of Health, who opened the discussion, said that it was generally agreed that there were few fields of medicine which had made more dramatic advances in the last 20 years than mental health. Indeed, there was now such a "new look" in mental health that it was no longer just a case of care and custody but of care and treatment, and in many cases cure. That fact was not generally appreciated. The workings of the mind, particularly the sick mind, were a very difficult subject for the man in the street to understand. There was still need to obliterate from popular speech such phrases as "padded cell," "put away," and "put in an asylum."

Why Bother?

Why bother about educating the public? So far as Parliament was concerned, vast sums of money could not be spent on mental health and priority could not be given to it unless people generally recognized the size of the problem and fully understood the need. The incidence of mental illness could not be kept down unless people were better informed and encouraged to come forward for treatment at an early stage. There must be a general realization that nursing the sick mind was just as important a service as nursing the sick body. The spread of knowledge of the principles of mental health would pay very handsome dividends. That had already been shown in the field of physical health, and the public now had to be persuaded that in safeguarding their physical health an essential concomitant was the safeguarding of their mental health.

Miss Hornsby-Smith added that she was well aware that the whole tendency to express scientific matters in colloquial terms was abhorrent to the average professional man, but if mental specialists were going to take the public with them they must give reasons understandable by the common man. And it was far better, if colloquial terms had to be used, that this should be done by those who were fully qualified than by the less skilled who might make a botch of it. She appealed therefore to mental health specialists to study the value and the best method of educating the public in their specialty. Mental specialists could not say too often or make too well known the fact that seven out of every ten who entered mental hospitals did so as voluntary patients and that the average stay of those discharged was just over two months. Recognition of such facts would help to build up in the mind of the public a better-informed picture of the service provided to-day.

Some of the Dangers

Dr. R. R. BOMFORD (The London Hospital) said that all doctors suffered to a considerable extent because they were expected to work magic; when their magic was successful they were irrationally praised, and when it was unsuccessful they were equally abused. He believed the mantle of the magician was now falling on mental specialists. Whilst there was a great deal of unconscious rejection of psychiatric theories for indefinite reasons, there was also a danger of people accepting psychiatry in an unreasonable fashion.

Dr. W. S. MACLAY (Board of Control) suggested that the many aspects of mental health needed to be more closely defined if there was ever to be a satisfactory assessment of the value of the effort and money expended on it. It was much easier for people to have sympathy with the aims of the mental hygienist than for the hygienist to be scientific.

Mr. FRANCOIS LAFITTE thought it would be helpful if all newspapers employed a competent medical correspondent.

Reports of Societies

TEACHING OF DERMATOLOGY

The teaching of dermatology for general practice was one of the subjects discussed at a joint meeting of the Sections of General Practice and Dermatology at the Royal Society of Medicine on February 16.

Dr. BERNARD PECK, speaking first, presented a strong case for improving undergraduate training in dermatology. Five to eleven per cent. of consultations were for skin disorders. In his own practice in Plymouth he had noted some seasonal variation, but on the average dermatological conditions accounted for 8.8% of all diagnoses. Reports on prescribing showed that some 12% of prescriptions were for skin preparations, and since this figure presumably included only local applications the actual percentage of prescriptions for the relief of skin conditions must be considerably higher. Of all patients referred for consultant opinions to a general hospital in Plymouth, 4.7% were referred to the dermatological department.

In most areas the opportunities of gaining knowledge of dermatology as a postgraduate were poor; and in any event Dr. Peck thought that it was not easy to acquire new knowledge after qualifying. A circular letter had been sent to the 27 medical schools in Great Britain. The 26 replies indicated a wide variation in the time allocated to dermatology in the undergraduate course. At some schools the same number of hours were devoted to dermatology as to radiotherapy and to thoracic surgery. Most schools allowed about 20 hours for out-patient demonstrations, and in only one were the patients for these specially selected. With very few exceptions most qualifying examinations did not regularly contain questions on dermatology, and, although an occasional skin condition might be included in the clinical examination, the knowledge required from candidates was likely to be superficial, since there were no dermatologists among the examiners.

In summing up, Dr. Peck suggested that an undergraduate training which ignored almost entirely one-tenth of the graduate's future work was unrealistic. He did not advocate any increase in the length of the present training, but felt that further time might be devoted to dermatology at the expense of the technical aspects of operative surgery and of other subjects which were not of such value to the future general practitioner. Moreover, apart from its direct importance to the practitioner, dermatology offered an excellent field for training in accurate observation and in the correlation of clinical and pathological findings.

Examination Questions

Dr. R. T. BRAIN, opening the discussion, said that dermatologists had long felt that the specialty had not received sufficient recognition in the medical curriculum. Dr. J. E. M. WIGLEY said that the fundamental problem was the lack of dermatological questions in qualifying examinations. Most students had perforce to concentrate on passing examinations, and until they knew that they would be examined in dermatology they would tend to be disinterested in the subject. There should always be a dermatologist on the board of examiners.

Dr. W. B. ADAM was critical of the postgraduate teaching in dermatology which he had received, and Dr. W. P. HEDGCOCK suggested that special training might be given during the period of trainee-assistantship. After several other speakers had taken part in the discussion Dr. C. H. WHITTLE pointed out that as a result of the shortage of registrars more appointments for general practitioners as clinical assistants in dermatology would probably become available. But Dr. M. FEIWEL thought that a practitioner derived much more benefit from sitting with a dermatologist in his clinics for some weeks than from acting as a clinical assistant seeing the old patients. Dr. G. B. DOWLING, from his experience of the postgraduate teaching of general practitioners, disagreed with Dr. Peck's implication that a general practitioner would not acquire much knowledge of dermatology from practical experience. He had found that many had gained a very sound knowledge of the subject. Dr. G. M. KERR, while agreeing that dermatology was inadequately taught, did not believe that this subject should be singled out for special consideration. The entire medical curriculum needed revision, because the general practitioner was taught very little about many other conditions which he frequently encountered in practice, including diseases of ear, nose, and throat, and of the eyes.

Nova et Vetera

AN EARLY X-RAY PICTURE

Last August Dr. Cochrane Shanks told in the *Journal*'s correspondence columns[1] the story of an early *x*-ray picture taken in March, 1896, by a 16-year-old boy, W. E. Davies. The boy was spending the Easter holidays in Hanover and had with him a quarter-plate camera. One of the local entertainments was a hall with side-shows, automatic machines, and the like, and among them was an automatic *x*-ray machine which, in return for a pfennig in the slot, showed up the bones of the hand or any other opaque object inserted through an aperture by the customer. On top of the machine was an eye-piece to look through. The boy, interested, as well he might be, in this novelty, and with a commendable scientific curiosity, visited the showplace armed with a sensitive quarter plate in light-tight box in which he had also placed some small metal objects. This he inserted into the apparatus, and, with the aid of the appropriate coins, gave it an exposure to the *x* rays of about one minute. The result (reproduced with Dr. Shanks's letter) was probably the first amateur *x*-ray photograph.

Dr. J. F. Brailsford[2] questioned the accuracy of the story. He pointed out that, though Roentgen made his discovery on November 8, 1895, he did not announce it publicly until December of that year. According to Glasser,[3] Edison, in May, 1896, was among the first publicly to demonstrate the fluoroscopic characters of *x* rays. It was remarkable, therefore, Dr. Brailsford thought, that the "show business" should be able to adopt this new scientific discovery so early as March, 1896. Reports of diagnostic skiagraphs first began to appear in the *British Medical Journal* in June, 1896, and in the issue for June 6 (p. 1412) it was announced that "a Roentgen laboratory has been established in the Glasgow Royal Infirmary."

The correspondence ceased after Dr. Brailsford's contribution, but the matter has not rested there. A Hanoverian reader of the *Journal* wrote to the editor of the *Hannoversche Allgemeine Zeitung*, who published the story and the doubts cast on it, and appealed to local memory. The response was immediate: the editor was able to publish the evidence of some 26 replies from senior inhabitants of Hanover who championed the accuracy of the boy photographer's story. One, Herr K., said that while he was in the fifth or sixth form at school he went to the exhibition, which contained the apparatus referred to. He was not certain whether it was in 1896 or 1897, but was in no doubt about the place where the exhibition was held. It was in a house in Georgstrasse, which is now the Basse Bank. Herr K. F. also could not quite fix the date, but added something to the story. "At the same time," he wrote, "there was also a Lilliputian married couple to be seen. The man was wearing Hussar uniform and had a big moustache and pointed beard, which we were allowed to pull to prove its genuineness." Herr K. M. wrote that he was an employee of the German Automaton-

Company, Stollwerk and Co., of Cologne, in 1900–5 at the house in Georgstrasse. He says that there were automatic chocolate machines, automatic music machines, electric pianos, weighing machines, the *x*-ray apparatus, automatic peasant bands, and a peepshow of the Frenchman Lumière. In the cellar of the house a cinematograph apparatus functioned from time to time. Although Herr K. M. could not confirm the year 1896, Herr B. S. produced the answer to the key question. He could say for certain that he had seen the *x*-ray apparatus in 1896 because he was married that year, and he had gone to the showplace with his new brother-in-law.

Further confirmation of the date 1896 came from a 78-year-old reader, Herr K. K., who became a soldier in 1897 and was quite definite that he went to the automaton show the year before. Dr. B. reported that in 1896 he already owned an *x*-ray apparatus in his practice, purchased through the firm of Nicolai, Leinstrasse, from Reiniger, Gebhard, and Schall. Herr O. R. also reported that a doctor in Gehrden owned an *x*-ray apparatus in 1896.

It seems, therefore, that Hanover and the show business were right up to date in March, 1896.

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3 *Wilhelm Conrad Roentgen and the Early History of the Roentgen Rays*, 1933. John Bale, Sons and Danielsson Ltd.

FLUORIDATION OF DOMESTIC WATER SUPPLIES

The Board of Faculty of Dental Surgery of the Royal College of Surgeons of England was asked some time ago by the Minister of Health to consider the question of the fluoridation of domestic water supplies. The following report was therefore drawn up, and last week it was accepted and approved by the Board of Faculty of Dental Surgery and by the council of the Royal College of Surgeons.

The Board is satisfied that the incidence of dental caries is much less among children and adults who have spent the whole of their pre-natal and post-natal life in areas where the drinking water naturally contains fluoride at a level of one part per million or more than among those in areas where the water is practically free from fluoride.

In 1945 the fluoridation of domestic water supplies for reducing the incidence of dental caries was started in certain selected communities in the United States of America and in one in Canada. Eight of these communities in which fluoridation was started from 1945–48 have been used as study centres. The results obtained each year have been compared with the base-line data, and in some centres, as an additional control, dental examinations have been undertaken in adjoining and comparable communities.

The evidence to date shows a reduction in dental caries incidence of 40% to 50% in children of the youngest age groups, which is comparable to what is observed in areas where the water has naturally a fluoride content of one part per million or more. In the older age groups the teeth have not been subjected to fluoridation during all their formative period, and the reduction is not as yet so marked. There is nothing to suggest that a water naturally containing fluoride has properties different from those to which fluoride has been added.

In a temperate climate, with a population of adequate nutritional standard, fluoride at a concentration of 1–1.5 parts per million as fluorine in the water produces an occasional white fleck on the enamel, but this cannot be detected without expert dental examination, and is found in only about 10% of children. The appearance of the teeth is excellent.

There is no scientific evidence of toxicity or of harmful effects in districts with the water supply fluoridated at this level.

The Board considers that there is very strong evidence in support of fluoridation, and welcomes the proposal that this procedure should be adopted in the first place in some selected districts that can be used as study centres.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Renal Biopsy

SIR,—Your leading article on renal biopsy (*Journal*, December 18, 1954, p. 1468) seems to us to imply that our technique of percutaneous biopsy of the kidney in the prone position is a simple matter which can be done by anybody. This is not so. We believe that indiscriminate use of the technique by untrained people will certainly lead to accidents. We feel that for the present the operation should be done only by those physicians or surgeons who are going to use the technique frequently as part of a programme for the study of patients with renal or related diseases.

Since our report[1] in May of last year we have done a further 150 biopsies, making in all a total of just under 200 biopsies to date. We have encountered no serious complications with our technique and have extracted adequate tissue for histological diagnosis in over 95% of our attempts at biopsy. The dangers of renal biopsy are retroperitoneal haemorrhage, severe laceration of the kidney, renal infarct, anuria, and spread of infection. We have been fortunate in that our only complications so far have been transitory renal colic in three patients, mild loin pain in six, and a sharp haemorrhage into the bladder in an old gentleman with severe calcific atherosclerosis.

In order to secure the safety of the patient, particular pains have been taken in the selection of patients, and meticulous attention has been given to their pre- and post-operative care. At present our contraindications for doing a biopsy are: an uncooperative patient, individuals with a bleeding tendency, patients with one kidney, and patients with oliguria whose non-protein nitrogen is above 100 mg. per 100 ml. of blood and rising. We do not advise a biopsy on patients who have severe calcific atherosclerosis, a perinephric abscess, hydro- or pyonephrosis, renal neoplasm, or large cysts. Although Cazal[2] has done a few biopsies on patients with renal neoplasm, we believe that the danger of spreading neoplastic cells along the needle track is too likely to warrant biopsy.

The hazards of kidney biopsy have been overcome by accurate localization of the kidney with intravenous pyelograms and the exploring needle, by the thin Franklin Vim-Silverman needle, which secures a small core of renal tissue without aspiration, and by the use of the sandbag in the prone position, which ensures post-biopsy haemostasis. Biopsy of the kidney is more accurate than any other method in making an exact diagnosis. There is no need to labour this point, but it must be obvious that, as time goes on, biopsy of the kidney will become more and more valuable as new therapeutic measures are found to combat each of the many disease processes which involve the kidney. We find that renal biopsy is a more accurate method than culture of the urine or blood in determining exactly the type of organisms which are responsible for infection within the kidney, and we have been using it to select patients with nephrotic syndrome for therapy with steroids. Besides its clinical value in diagnosis, prognosis, and therapy, it is a most valuable tool for studying the natural history of diseases of the kidney.

We have already trained a number of British physicians to do biopsies of the kidney in the prone position, and we look forward, as you do, to reports on its usefulness.—I am, etc.,

Chicago, 12, U.S.A. ROBERT M. KARK.

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Misuse of Penicillin

SIR,—The spectacular effect of penicillin in the treatment of certain severe acute infections, and recently increased availability, have led to the use of this drug on a large scale in comparatively mild respiratory infections. It is sometimes forgotten that penicillin does not suit some individuals, and it is likely that we shall see a variety of patients who are complaining of symptoms which could be referred to the treatment which they have undergone.

In recent years, in particular during the present winter, I have seen a number of adult patients who complain of asthma which they date from a minor respiratory infection, usually labelled a "chill" or "bronchitis." The common factor in these cases appears to be that all have received penicillin, usually by injection, but sometimes by inhalation. Skin tests in several of these cases have demonstrated sensitiveness to penicillin, and in other cases I have found a positive skin reaction to the Bencard group of moulds. There seems little doubt that penicillin may provoke an onset of asthmatic symptoms in patients who are sensitive to it, and the treatment of the sequel may be much more troublesome than the treatment of the initial complaint.

It would seem, therefore, that care should be exercised in the selection of patients who are regarded as being suitable for penicillin treatment. It is my impression that the milder infections respond quite well to the methods of treatment which were used before penicillin was discovered.—I am, etc.,

London, W.1. JAMES MAXWELL.

Chlorpromazine

SIR,—Clinical investigators are entirely dependent on the laboratory work of our colleagues the pharmacologists. It is disconcerting when two sets of workers apparently meet in head-on collision (*Journal*, February 5, p. 338). The experiments of Holzbauer and Vogt[1] in Edinburgh and the Frenchmen Aron, Chambon, and Voisin[2] are not, however, comparable. The French workers performed a neat and simple series of experiments; they removed one suprarenal from unmedicated rats and estimated the ascorbic acid content. This was the control, and also constituted the stress. An hour later the other suprarenal was removed, and the fall in ascorbic acid noted. In another series of rats, chlorpromazine was given at varying times before the first operation, and the two operations repeated as before. The fall in the ascorbic acid content of the second suprarenal was found to be considerably less in the animals that had chlorpromazine. From these results they reasonably concluded that the drug modified the normal effect of trauma on the suprarenal ascorbic acid content. They were careful not to claim that the drug caused a chemical hypophysectomy.

In Edinburgh the animals were medicated with urethane. A laparotomy was performed. An hour and a half later the animals were killed while still anaesthetized and the ascorbic acid content of both suprarenals estimated. In another series of animals they were given chlorpromazine prior to the experiment. This made little difference to the fall in the ascorbic acid content of the suprarenals. This experiment shows that, in rats given urethane, trauma causes a fall in the ascorbic acid content. Chlorpromazine added to the urethane does not modify the fall to any greater extent than does urethane itself.

We must be careful not to apply results found in rats at dosage of 10 mg. per kg. to those obtained in man at a dosage of less than 1 mg. per kg.

Pronouncements about this drug show laudable *ex cathedra* negativism, but the details of the experiments on which the findings are based should be more widely known.—I am, etc.,

London, N.W.1. ANGUS SMITH.

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SIR,—Your recommendation of caution in the use of chlorpromazine should certainly receive careful consideration by all those who have found this drug useful and employed it extensively. For three or four months I have been giving it to patients suffering from dermatoses in which the mental aspect was deemed to be of importance, and I would estimate the incidence of jaundice at no more than two cases in about one hundred.

The first patient phoned my clinic one day to report that he had developed shivering attacks eight days after being put on 25 mg. of the drug three times a day. On the following day he noticed dark urine. I subsequently confirmed from his family doctor that he was suffering from jaundice. The second case developed after 24 days on an identical dose. The patient developed vomiting followed on the next day by dark urine. As he was feeling so much better generally since taking the drug, he continued taking it until seen three days later, when he showed marked clinical jaundice.—I am, etc.,

London, W.1. W. G. TILLMAN.

Lead-poisoning

SIR,—The papers by Drs. J. W. G. Gibb and J. F. MacMahon and by Dr. H. B. Marsden and Miss V. K. Wilson (*Journal*, February 5, pp. 320 and 324) rightly emphasize the disastrous consequences of lead-poisoning and the difficulty of early diagnosis. Even when lead-poisoning is suspected, it is often not easy to obtain confirmation, particularly in those mild cases whose prospects for successful treatment should be brightest. Isolated examinations of the blood for stippled cells or of the urine for albumin and sugar may be negative, radiological changes may be inconclusive, and lead assays in blood or urine are impracticable as a screening test. In these circumstances, the qualitative test for urinary coproporphyrin is valuable. This consists in adding 5 drops glacial acetic acid, 3–4 drops of hydrogen peroxide, and 1–2 ml. ether to 5 ml. of urine in a test-tube: after 10 minutes the tube is inspected in a "Wood's light." If excess of coproporphyrin is present, there is reddish-pink fluorescence of the ether layer. The test is a simple one requiring little time; it is generally positive in active lead-poisoning and sometimes may be the only readily demonstrable sign. Coproporphyrinuria of course occurs in certain other conditions, but none of these is likely to be mistaken for lead-poisoning.

As Drs. Gibb and MacMahon remark, children who have recovered from acute lead-poisoning remain during childhood and adolescence (because of skeletal storage of lead) in a precarious plight. However, since the introduction by Bessman *et al.*[1] in 1952 of treatment with the chelating agent calcium disodium ethylenediamine tetra-acetate (calcium disodium versenate) it is no longer correct to say that "successful therapy merely diverts lead to the bones." There is much evidence that, in addition to relieving the symptoms of acute plumbism, calcium disodium versenate therapy increases the total excretion of lead from the body, and in fact leads to *removal* of lead from the bones.—I am, etc.,

London, W.2. H. McC. GILES.

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Silver Stool Sign

SIR,—I was greatly interested by Sir Heneage Ogilvie's memorandum (*Journal*, January 22, p. 209) concerning the silver stool sign, and by the correspondence which has followed it. Twice during the past six months I have been shown silver stools. On one occasion the stool was well formed and had a distinctly metallic sheen. The production of such a stool was an isolated occurrence in a patient who had had a myocardial infarction and was being treated with phenylindanedione.

The other and much more remarkable event was the production of an "aluminium paint stool," which I think must have been exactly similar to that described by Dr. Arnold S. Aldis (*Journal*, February 12, p. 414). The bright silver

appearance of the exterior of this stool was only slightly less marked throughout its substance.

The patient concerned, a man aged 58, had been admitted to hospital five days previously, complaining of severe substernal pain since the preceding day. He gave a history of anginal pain for three months, and fifteen months before he had been admitted to the same ward because of a severe melaena. Radiological examination following this episode showed no evidence of gastric or duodenal ulceration. The more recent event was diagnosed as a myocardial infarction and this was confirmed by E.C.G. Anticoagulant treatment was started with ethyl biscoumacetate. On the same day as he produced the silver stool, the prothrombin time was 8.8 times normal and the prothrombin index was 11. Anticoagulant treatment was stopped, and by this time he had received a total of 3.6 g. tromexan. On the seventh day after admission his condition suddenly deteriorated and he died. No more silver stools had been passed. Post-mortem examination confirmed the presence of a large postero-septal myocardial infarct which was thought to be about three weeks old. Because of his history of melaena the gastro-intestinal tract was carefully examined. There was no evidence of past or recent haemorrhage or ulceration, nor was there any macroscopic evidence of neoplasm. The pancreas appeared normal, as did the other viscera.

If a silver stool is evidence of altered blood in the gastro-intestinal tract, then I feel that the production of silver stools by two patients, both of whom were being treated with anticoagulant drugs, may well be significant, and such an occurrence should be regarded as an indication for increased caution in the handling of these drugs. I should be most interested to know whether others have noted a similar association.—I am, etc.,

Carshalton. JOHN WEEKS.

S.T.H. and Tuberculosis

SIR,—In his lecture on "The Role of the Host in the Chemotherapy of Tuberculosis," reproduced some time ago in the *Journal* (October 2, 1954, p. 767), and which I read otherwise with much interest, Dr. P. D'Arcy Hart mentions our work in the following terms: ". . . We have been unable to antagonize the protuberculous effect [of cortisone] by any structurally similar steroid; and although Lemonde *et al.* have claimed to have done this with somatotrophic hormone (S.T.H.) in rats, and even to suppress experimental tuberculosis in mice with this hormone, we have failed to produce either effect in mice."

I feel that the author exaggerates a little. It is true that we have found, in repeated experiments, that the somatotrophic hormone (S.T.H.) prevents the extension of tuberculous infection, catabolism, and death in cortisone-treated rats, but we never claimed to suppress tuberculosis in mice with S.T.H. What we saw is the following: (1) In mice affected with a stable, chronic form of tuberculous infection, S.T.H. decreased the number and extent of pulmonary lesions, as well as the number of bacilli in the lesions.[1 2] (2) With a rapidly evoluting disease—whether this was achieved by inoculating a larger amount or a more virulent type of bacilli or by treating the animals with A.C.T.H.—and in spite of the fact that we repeated the experiments several times under various conditions, we never succeeded in obtaining any prolongation of survival, even though the lesions and the number of bacilli were generally reduced.[3]

May I add that a group of investigators, working with the guinea-pig, have reported recently some results which are in accord with ours—i.e., that S.T.H. diminished the extent of tuberculous lesions[3] and potentiated the action of isoniazid.[4]—I am, etc.,

Montreal, Canada. PAUL LEMONDE.

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2 —— and Panisset, M., *Amer. Rev. Tuberc.*, 1955, **71**. In press.
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Tuberculous Mesenteric Adenitis

SIR,—I was much interested in the account given by Dr. H. R. E. Wallis of tuberculous mesenteric adenitis in children (*Journal*, January 15, p. 128), because of the enormous contrast between past years and now. Referring to Colt and Clark,[1 2] who dealt chiefly with adult cases, we described some surgical aspects of tuberculous disease of the abdominal lymphatic glands. There is an excellent, brief, comprehensive, and easily accessible abstract of the relevant parts of the latter paper in the *British Medical Journal*.[3] G. N. Clark is not now in England and cannot join with me in this letter.

In those days the condition of the udders of the cattle on the farms was bad. Tuberculin-tested herds were supposed to yield milk that was free of tubercle; indeed one herd has never been known to show infection since then, but two fatal cases of tuberculous meningitis were admitted to the Sick Children's Hospital on the day that one of our patients came under our care. This patient, aged 5 years, had been looked after at home and fed on boiled milk until put on certified milk. Acute peritonitis very soon followed with temperatures of 101°–103° F. (38.3°–39.4° C.) daily for 13 weeks, and marked ascites. Now, after 20 years of married life and with no detectable disability, the patient remains sterile. On two occasions doctors have suspected appendicitis, but, as will be shown presently, operation has been avoided.

At that time there was prejudice and fear amongst the farmers that they would lose on compensation and on their established reputations in the markets. Once these items had been adjusted there was a great improvement, but it was not sufficiently rapid to appear in our articles. I believe that a good co-operative drive at that time would have eradicated the disease in about two years. Why after all this long time the disease has not been completely eradicated is difficult to understand, but Dr. Wallis's article shows that it has not. Importation of cattle may be a factor.

Our articles were as complete and comprehensive as could be attained at the time. They dealt with 239 consecutive cases admitted into a general adult surgical ward, many of them—in fact most—as abdominal emergencies. 207 of the cases were traced and 118 patients were seen and examined. In 38 caseous cases the patients were operated on. In the later calcified cases, as well as in the caseous, the presence of acetone in quantity in the breath (which does not seem to have been noticed by previous observers) was so common that this alone was sufficient and safe to enable urgent operation to be avoided. Hyperaesthesia and increased tonus of the muscles in the right iliac fossa, though more diffuse and less intense than in appendicitis, were not so certain in their indications. Lockwood's sign always proved invaluable, and on one occasion it was possible to actually demonstrate its mechanism on the exposed viscera, which I do not think Lockwood actually did.

Now that the State pays for radiological investigations and facilities have also improved, it would be a great help in coming to a decision to be able to observe, by serial *x*-ray examination, the rate of calcification of glands and whether there is any difference in the rate of deposition of calcium when either milk is fed or any of the other more modern preparations. Judging by our observations it is impossible to be sure of the facts by ordinary clinical methods, palpation and so on, but with careful adjustment of tests with *x*-ray tubes it should be possible to obtain comparable pictures of the amount of calcium present. Some of the aluminium alloys should match up the degree of opacity. In former days no two tubes could ever be made to give comparable results on the same day, and even the penetration of one tube varied with its temperature. The difference in fuzziness of the dendrons is important as well as the gross density of calcification.

If this letter has re-established a link with our articles, which were comprehensive, and gave a chronological approach to the subject by the references, it will be of some satisfaction, because it will help to demonstrate the great advance in the factors of the state of the public health which have come about in the last 15 years. For details the papers themselves should be consulted.—I am, etc.,

London, W.1. G. H. COLT.

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Treatment of Pulmonary Tuberculosis

SIR,—Artificial pneumothorax began to lose popularity as its complications became widely appreciated and as surgical alternatives multiplied. Dr. J. L. Livingstone (*Journal*, January 29, p. 243) considers that it still has a limited place in the treatment of tuberculosis, especially since chemotherapy is likely to reduce the complication rate; and you, Sir, in a leading article of the same date (p. 273), find it difficult to believe that it "can really have no useful part to play in the future."

I myself do not think that there is any place for artificial pneumothorax treatment to-day, and hardly any for pneumoperitoneum. The disadvantage of having to attend a doctor every week or two for air refills is one of which little was made when alternative methods were few. Yet it is in fact so considerable that, even if no risk whatever were involved, the physician should seek other methods wherever practicable. No one would deny that artificial pneumothorax has had good results as well as bad, but other methods are making it redundant. Current developments in the use of chemotherapy appear to be giving as good results, or better, in every respect, and it is my view that all forms of pneumatic treatment should now be abandoned as not having merit enough, compared with prolonged chemotherapy, to set against their obvious disadvantages. Only if some unforeseen snag is discovered in the use of chemotherapy for long periods should we consider reopening the refill clinics.—I am, etc.,

Malvern. T. W. LLOYD.

Treatment Abroad of Tuberculous Children

SIR,—This association is having considerable success with sending British tuberculous children for treatment at Vordingborg Sanatorium, Denmark. In the last three years some 235 children have been sent across, with exceedingly good results. At the present moment 47 patients are under treatment at Vordingborg.

It is true, as Dr. F. J. Bentley says (*Journal*, February 12, p. 418), that there is less need for treatment abroad than there was a few years ago, but we find that from Clydeside, Merseyside, and Northern Ireland there are still children whom the chest physicians wish to send. This Anglo-Danish scheme is free of cost to the parents or our Health Service. Children are kept at Vordingborg at the expense of Anglo-Danish sympathizers. The whole scheme owes its origin to the success which Denmark has had in eradicating childhood tuberculosis, and which has set free beds in the sanatoria. The psychological benefit to these children of a stay abroad during the impressionable years of life is certainly not the least important part of the scheme.—I am, etc.,

London, W.C.1. HARLEY WILLIAMS,
Secretary-General, The National Association for the Prevention of Tuberculosis.

Paraffin Stoves

SIR,—In these days of expensive fuels there is an increasing tendency to use paraffin-burning stoves in sickrooms and living-rooms of domestic dwellings. It appears that this method of heating is not without danger. A few days ago I was called to see a man and his wife of 40 years of age who had retired to bed in excellent health the night before and had been found by neighbours at 11 a.m. the following day in very bad shape. When I arrived at the house the woman was still in bed and comatose. The husband had managed to crawl downstairs in answer to repeated and persistent ringing of the doorbell. He was very weak and drowsy and complained of headache. In the bedroom was a small paraffin stove of modern design which had been allowed to burn throughout the night. The bedroom door had been tightly closed, also the window, and the only ventilation was by means of the chimney. Fortunately the stove had run out of paraffin, otherwise a tragedy might have resulted. The stove had used up oxygen and had given out carbon monoxide.

It appears that the general public is largely unaware that any harm can result from an oil stove burning in a confined space. I suggest that a word of warning by the doctor finding one in a sickroom might not be out of place and might help to prevent serious and even tragic results.—I am, etc.,

Blackburn. F. C. REIDY.

Fluoridation of Public Water Supplies

SIR,—Dr. A. M. Thomson's letter (*Journal*, January 22, p. 224) provides an excellent example of the methods by which fluoridation has been promoted—namely, by sweeping assertions of knowledge in matters in which more cautious, or perhaps more humble, people admit their ignorance, supplemented by attempts to discredit opponents by a display of contemptuous language. It would have saved much trouble if the mission to the U.S.A., of which Dr. Thomson was a member, had presented both sides of the question fairly instead of behaving as a team of advocates for the proponent side. According to the report[1] of this mission (p. 11) the case against fluoridation was given full prominence while they were in the U.S.A. at the hearings before the Delaney Committee.[2] This committee, in fact, examined eighteen scientific witnesses, of whom seven were critical of fluoridation. Nevertheless, there is no evidence in the mission's report that they had visited or consulted any of these scientists; and, although a few words of the Delaney report are quoted and some criticisms of fluoridation are mentioned with a view to refutation, it is quite clear that the opposition case has been seen only through the eyes of its opponents. This bias is even clearer in Dr. Thomson's letter; and when it comes to the *ex cathedra* statements of public health officials there is no attempt to present the opposition case to the public, which is why persons such as myself have had to take a hand in the matter.

I cannot see what Dr. Thomson gains by jibbing at a plain accurate description of what he advocates. If "medical treatment" is limited to "cure" and excludes "prevention," the "medical" profession can have no status in the matter. If dosing everybody with something required only by children is not "indiscriminate," what is? Or does he hold that the scientific "discrimination" exercised in putting the fluorides in the right reservoir is sufficient? And I fail to see why this medical Big-Brotherism, with its insistence on invading every home and everybody through the water tap, should be regarded as "scientific," and an objection to it as "unscientific," except, of course, for propaganda purposes. Nice as it is to find the *North Wales Chronicle* so carefully read in Aberdeen, I think he was unwise to drag into this discussion from its pages a reference, quite correct in its context, to "civilized European opinion" and to the precedents for medical tampering with the human body without consent. The ten standards laid down at the Nuremberg trials on August 9, 1947, for persons who initiate or engage in medical research on, or treatment of, human beings, start with this statement: "*The voluntary consent of the human subject is absolutely essential,*" and I have yet to learn that the British medical profession regards itself as exempt from this standard of conduct. In France, I am informed, the Dental Convention in Paris has recently rejected fluoridation as contrary to human rights, local governments have no power to order it, and the Institut Pasteur and the Ministre de Santé Publique have not approved it.

If it is true, as Dr. Thomson clearly implies, that the medical profession, which is not without experience with dangerous drugs, can yet find no safe way of administering fluoride, under normal conditions of consent, only to those who may be expected to benefit, I cannot see how the public can be expected to consent to the putting of this substance in the general water supply. The statement that "variations in the amounts of fluoridated water ingested by individual consumers are known to be without significance for health" would be sufficiently staggering if the word "fluoridated" were omitted. With the bottom limit for "chronic low grade poisoning" officially placed as low as

2 mg. daily, as compared with 1 to 1.5 mg. of fluoride daily for "preventive dentistry,"[3] it makes no sense to me.

Finally, I come to the actual evidence upon which the proponents of fluoridation base their astonishing claims to knowledge of its harmlessness to individuals. The evidence is almost entirely statistical, and, considered as such, unconvincing to the point of absurdity. The Bartlett–Cameron comparison reviewed in your annotation "Fluoride in Water" (*Journal*, January 22, p. 215) seems to be, to date, the most careful long-term investigation into the effects of fluorides upon health, other than dental decay. But here we find, not the "evidence from millions of people" mentioned by Dr. Thomson, but a comparison of two populations of about 120, of an age-distribution so different that 14 deaths in one is not significantly different from 4 deaths in the other. Just to make it funnier, the younger population turns out to have nearly twice the incidence of cardiovascular disease found in the older, and, to round it off, the water of the "control" town has more than the average amount of fluorine in it (0.4 p.p.m.). Certainly it is quite true to say that this comparison has produced no evidence of damage due to fluoride at 8 p.p.m., but such a statement is completely misleading unless accompanied by an estimate of the number of people in Bartlett who would have had to suffer death or observable damage through ingesting fluoride in order to produce a significant result. It seems obvious, even on the limited data available, that, with samples of this size and variability of this order, the disaster to health in Bartlett would have had to have been catastrophic to have reached statistical significance. So far as I know, no one has entertained the idea that fluoride at such low concentrations could produce damage of that kind, so that the "evidence" is entirely irrelevant to the question of the possible hazards of fluoridation. The mortality statistics for 22 Illinois cities, published in the British mission's report[1] (p. 62) are equally unconvincing. The only thing demonstrated is the irrelevance of the statistical approach to this matter.—I am, etc.,

Bangor. C. G. DOBBS.

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Slippery Floors in Hospitals

SIR,—May I draw attention to a subject which receives very little? I refer to the large number of minor and major accidents which occur to the staff and patients of hospitals, many instances of which I can quote, including fractures of limb bones, due to slippery floors. Most hospitals have some system of recording such accidents because of possible litigation, and when injury is caused this process is usually carried out, but many more accidents causing damage to hospital property, mainly crockery, glassware, and thermometers, due to nursing and domestic staff slipping in wards or ward annexes, probably go unreported. When post-operative patients, the infirm and aged, and those recovering from limb fractures are being encouraged to get on their feet, there is in most of them a natural loss of confidence resulting in muscular incoordination, and a slippery floor is the worst possible surface on which to try their first hesitating steps; not only are their feet liable to slip but also their walking-sticks or crutches, with resulting falls. The lethal effect of fractured neck of the femur in the aged is of course well known.

A tendency to slip depends on several factors, which briefly are those associated with the person, such as some locomotor disability and also the material composing the soles and heels of his footwear, and factors relating to the composition, texture, and polish of the floor. The problem is a difficult one, because some shoe surfaces will slip on some flooring materials and not on others, but in my view much of the trouble is caused by the excessive and unintelligent use of floor waxes and polishes, so as to produce the shining appearance beloved by administrative nursing staff. Polish which is claimed to have a non-slip quality is, I believe, available, but the accepted view seems to be that if it is non-slip it cannot polish. I suggest that this is a problem of some importance which deserves the attention of hospital architects and administrators. Slippery floors in hospitals are a serious hazard to patients and staff and they should no longer be tolerated.—I am, etc.,

London, N.W.9. W. E. SNELL.

Ward Rounds and Myocardial Infarction

SIR,—I was much interested in Dr. Klaus A. J. Järvinen's article (*Journal*, February 5, p. 318). The importance of his findings on the unfavourable response of patients with acute myocardial infarction to the hazards of hospital routine can hardly be exaggerated. The emotional stress causing a fatal issue in six of his patients is perhaps too narrowly defined as the result of the visiting physician's ward round, many other factors—partly mentioned by the author—connected with the daily hospital experience of such patients combining in the production of an anxiety state so dangerous for those affected with coronary artery disease.

But does not the logical conclusion present itself that such a patient is best treated in his own home whenever circumstances permit? In an extensive cardiological practice, before I came to this country, I had made it a rule to treat all my patients with acute coronary occlusion in their home, in surroundings best suited for safeguarding mental rest, and had no cause to regret this procedure. Only so is it possible to disguise the diagnosis in spite of the difficulty of persuading the patient to keep his six weeks' absolute rest. Though often enough, owing to socio-economic conditions, I had to dispense with the expert help of a day and night nurse and had to entrust the care of the patient to a reliable member of the family, the results were satisfactory and the mortality rate among my patients was considerably low. The small inconvenience of taking my portable electrocardiograph to the patient and of performing simple laboratory tests like E.S.R. and urine examinations at the bedside was highly compensated for by the beneficial effect of allowing the patient to remain in his familiar surroundings.

It must, of course, be admitted that modern anticoagulant treatment may make it difficult for the practitioner to decide in favour of this management, but I am certain that many general practitioners will agree with me that, provided all available facilities are used (and the home help service should be mentioned in the first place), home treatment can be assured with benefit to the patient in the majority of cases. As a mere onlooker I feel hardly entitled to comment on the value of anticoagulant therapy in coronary artery disease, a treatment unknown in the 'thirties, but do the results so far obtained really justify the frequent unavoidable risks of interfering with the patient's most-needed rest? Four patients of the six cases reported in Dr. Järvinen's paper had died in spite of anticoagulant treatment.—I am, etc.,

Leicester. LEO HAHN.

Treatment of Phenylketonuria

SIR,—We have read with great interest the important paper, "Treatment of Phenylketonuria with a Diet Low in Phenylalanine," by Dr. L. I. Woolf, Dr. Ruth Griffiths, and Professor Alan Moncrieff (*Journal*, January 8, p. 57). The psychological findings provoked a great deal of discussion here, during which we felt that certain aspects should have been taken into consideration before placing too much reliance upon the apparent improvement in intellectual level in the three cases involved in the investigation. It is known that mentally defective children are subject to fluctuations on their test scores, and any extra attention on the part of

the investigators might easily have produced some improvement. A control group in this case would have been very desirable. The prediction of educability based on pre-school tests, to which Dr. Griffiths's valuable test belongs, is not highly reliable, because of their nature. Allowance should be made for practice effect on the same test and also for improvement in adjustment to the test situation with repeated testing. We look forward with much interest to further findings.—We are, etc.,

J. G. HOWELLS.
W. PAWLIK.

Ipswich.

Disk Lesions and Low Backache

SIR,—When reading the paper by Dr. James Cyriax (*Journal*, January 15, p. 140) I felt certain it would provoke a lively correspondence; this has proved to be the case. While thoroughly agreeing with Dr. Cyriax that manipulation or traction is often successful in the treatment of acute and chronic back conditions, I think it should be recognized that such treatment, even in the most expert of hands, sometimes makes the patient worse.

Being quite unable to accept the contention of Dr. Cyriax that practically every case of low back or sciatic pain is caused by a disk lesion, I was delighted to read the letters of Mr. W. Grant Waugh and Dr. A. C. Elkin (*Journal*, February 12, pp. 412 and 413), pointing out the importance of the apophyseal joints as a source of low back and sciatic pain, for I have long held similar views.[1] The fact that one can so often give the patient relief by a single manipulation, in my opinion, makes it exceedingly unlikely that a disk protrusion could be the cause of the symptoms. The nucleus is contained within the annulus under very considerable pressure, and, although it is easy to visualize lumbar traction reducing the protrusion, it is difficult to understand why the protrusion should not recur as soon as traction is released. If anyone doubts the importance of the posterior joints as a source of low back or sciatic pain I would suggest they read the papers by Putti,[2] Kraft and Levinthal,[3] and Harris and MacNab.[4]

We should beware of "omnibus" diagnosis and treatment. Mr. Grant Waugh rightly points out that the intervertebral articulation comprises three elements—the disk, the spinal ligaments, and the apophyseal joints—and that any pathological condition which affects one affects all. Therefore if we must have an "omnibus" diagnosis let it be "intervertebral derangement."

As for treatment, each and every case should be considered on its merits. Many cases recover with rest alone, while others do equally well with physiotherapy. Though manipulation or traction often provides a short cut to recovery, there are exceptions, and for these cases the plaster jacket still remains the most effectual remedy. Furthermore, if one had succeeded in reducing a disk protrusion by traction, it would appear rational to follow up with a plaster jacket to enable repair to take place and prevent recurrence. Fortunately Nature is very wonderful, and many patients recover "in spite of" rather than "because of" what we do for them.—I am, etc.,

E. J. CRISP.

London, W.1.

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SIR,—Mr. John Charnley's admirable article on this subject (*Journal*, February 5, p. 344) imparts a constructively sane approach towards this condition. As a G.P. surgeon I can testify to the cost and burden borne by the hospital and general-practitioner services since the British public began to take lumbago and sciatica seriously. Shortly after the war I worked for two years as a clinical assistant in the orthopaedic department of my old teaching hospital. Droves of patients with varying degrees of backache clogged the department. One of the two consultants, who was contemporary with me as a student, asked me: "As a G.P., what did you do with all these cases before the war?" My reply was: "Before the war these cases did not exist. Severe sciatica was relatively rare, while lumbago, though common enough, was not regarded seriously either by doctor or patient, and they soon got well."

It must be agreed that we had no satisfactory explanation for these conditions, or for "fibrositis," "neuritis," etc. Now that we have a logical explanation, I cannot agree too much with Mr. Charnley's recommendation that a robust attitude by both doctor and patient towards this tiresome condition will do much to reduce invalidism and waste of time and money in the Health Service. Dr. James Cyriax has, without doubt, hit on a line of therapy which works in a large number of cases. One cannot, however, help retaining some scepticism with regard to the claims for so many instant cures, on a purely physical basis. Successful psychotherapy *does* produce instant cure in all the faithful, and one wonders whether indeed many of Dr. Cyriax's cases lie in this category. "Laying on" of healing hands. . . ?

It is to me certain that many "backache" cases are psychologically inadequate and conform to a psychosomatic type easily recognized in general practice. Mr. Charnley mentions fluid retention in the nucleus pulposus as the cause of increased tension, and associates glaucoma in the comment. Glaucoma is undoubtedly psychosomatic in many cases. May it be that further research into the biochemistry and endocrinology of localized fluid retention will shortly provide that link between mind and body which will present both practitioner and patient with a satisfactory explanation for these and allied states?—I am, etc.,

L. DULAKE.

Reigate

SIR,—Although a personal admirer of Mr. John Charnley's attitude to chronic backache (*Journal*, January 15, p. 163), I find it very hard to be convinced over his explanation of acute lumbago on a disk basis. To me the fulminating onset does seem quite easily explicable on an inflammatory basis, since the pain is not due to ordinary inflammatory tension but to a sudden cramp in the affected muscle. Anyone who has ever had acute lumbago will never forget the tightening up of the muscles in the excruciatingly painful spasms. These painful cramps occur in other conditions where muscles are irritated, which we all know of and where no disk lesion is in question, such as in cold (ranging from cold sheets to cold water—where it can cause drowning) and in anoxic states. One would like to know how Mr. Charnley would explain on a disk basis the exactly analogous condition of stiff neck, where the intensely painful spasm is on the side that was exposed to the draught. Unless he can explain this, it is hard for one to be convinced over the acute lumbago. Needless to say, I am not referring to the syndrome of an acute disk lesion, which is often accompanied by trauma, and where the pain shoots down the leg and is a longer time going away, and still less to chronic backache. I am merely referring to the ordinary attack of acute lumbago that disappears completely.—I am, etc.,

T. L. CLEAVE.

Alverstoke, Hants.

SIR,—As a general practitioner the question of backache has always been of great interest to me, and the recent articles and letters in the *Journal* have prompted me to tell of another line of approach that I have taken.

I have found that a good number of patients trace their backache to some previous injury or sprain. As so many people can explain almost everything from a boil on the nose to a carcinoma of the breast by a blow they once received, I determined to follow up a number of cases of minor injury to the back and see whether the patients returned complaining of backache. In some six years I have managed to collect 60, mostly young, people who have had minor sprains and injuries to their backs. Each case was carefully examined and charted on a diagram—the greater the tenderness the bigger the spot on the diagram.

I divided them into three groups : (1) *24 Cases :* Treated with rest, heat, aspirin, and some massage. Allowed to return to work when they felt they "could make it." No further instructions given to them. Of these, 20 returned within weeks or months complaining of backache, and 18 had their chief tenderness localized to the area of previous tenderness as marked on the diagram—especially in the "big spots." (2) *26 Cases :* Treated in same way as (1) but told about my chart and asked to return if backache returned. Of these, 18 returned—all with pain in the marked areas. (3) *10 Cases :* These were made to rest till all signs of pain had gone—given more prolonged massage. Told to return at slightest suggestion of pain. Only one returned.

It seems, therefore, that a case can be made out for not "neglecting" minor injuries to the back as a means of preventing some cases of backache.—I am, etc.,

London, W.7. A. M. LASNICK.

Hyperpyrexia and Anaesthesia

SIR,—Dr. R. Cecil Brown (*Journal,* December 25, 1954, p. 1526) has given an interesting account of hyperpyrexia and convulsions occurring in a patient anaesthetized with thiopentone, nitrous oxide, and trichlorethylene. It is well known that carbon dioxide can produce cerebral congestion and convulsions. The high metabolic rate associated with hyperpyrexia and a convulsion would result in increased carbon dioxide production, and it would be interesting to know how much was given, and for how long, in the treatment of the laryngeal stridor.—I am, etc.,

Newcastle-upon-Tyne, 4. J. D. WHITBY.

The National Formulary, 1955

SIR,—There will be widespread agreement with your leading article (*Journal,* February 12, p. 402) on the new edition of the *National Formulary,* but to say that the committee's decision to revert to Latin for group and individual titles "will undoubtedly occasion some controversy" is indeed an understatement. It is quite incredible that the 1955 committee should reverse in its tracks. Instead of, as outlined in the preface, completing the change-over to "a more rational grouping and transition to the use of English in prescribing, in conformity with modern trends," it has decided that because the 1952 compromise was "unwelcome to the majority of those who use the *Formulary*" therefore the next rational step is to retreat to Latin instead of to advance logically to the adoption of English throughout the *Formulary.*

This reversion to a traditional although outmoded pharmaceutical convention involves the ridiculous pseudo-Latinization of approved names of drugs ; cyanocobalamin injection is a sufficient mouthful without the absurdity of injectio cyanocobalamini being substituted for it. Furthermore, it is completely unreal to attempt to justify the step by pleading that the Latinization of drugs makes them thereby more easily understood internationally. A prescription written for inj. insulin. protaminat. c. zinc. is no more easily interpreted in Chile or China than protamine zinc insulin injection. The argument that a national *Formulary*—which is in daily use in town and country, general practice and hospitals, throughout the United Kingdom—must be in Latin because the *Pharmacopoea Internationalis* is in Latin is as absurd as to maintain that the key and explanations at the foot of Ordnance Survey maps should be in Latin because many foreign tourists visit this country. In any case, the national equivalent to the *Pharmacopoea Internationalis* is not the *National Formulary 1955,* but the *British Pharmacopoeia 1953*—which has adopted English usage. It would be amusing to discover how many, or rather how few, prescriptions are in fact written in this country and subsequently presented to foreign pharmacists. No, Sir, neither by this nor any other hackneyed argument, such as the necessity to conceal the contents of a prescription from a patient, can this reactionary, retrograde, and misguided decision be justified. There is no place in modern medicine for such rigid adherence to pharmaceutical tradition, and few, if any, medical schools throughout the country train students to prescribe in Latin. Many doctors will therefore welcome the proposed edition of a companion volume to the *Formulary* in which English is to be used throughout, and the formulae grouped according to their pharmacological classification. Such a formulary will meet with more general acceptance, and would be the appropriate guide for young doctors starting practice uninfluenced by previous contact with the archaic mystique of Latin prescriptions.—I am, etc.,

Edinburgh, 3. ALASTAIR G. MACGREGOR.

SIR,—Your leading articie (*Journal,* February 12, p. 402) on the above publication surely reflects the views of the majority of practitioners. It is inevitable that a book of this nature will not meet with the approval of all its readers in every respect. Difference of opinion is understandable, but inconsistency is not. The declared policy of the Joint Committee is to include "a preparation even if its justification on pharmacological grounds is disputed, if it is still being frequently prescribed." Why, then, is bismuth carbonate not included among the remedies for dyspepsia ? Much has already been written concerning the relative merits of antacid preparations, and one must accept that difference of opinion exists. In 1949 the Committee suggested analogous preparations were as good as bismuth carbonate : they did not categorically deny it to be of value. The question as to whether bismuth carbonate is frequently prescribed cannot be a matter for conjecture when the overall consumption of bismuth carbonate in this country is increasing.

There is every indication that bismuth carbonate is frequently prescribed, and this warrants its inclusion in the *National Formulary.* If there is some other reason for its exclusion, then the Joint Committee should make it perfectly clear, for their present attitude is inexplicable and lacking in logic. Those who have found bismuth carbonate of value will no doubt be disappointed at its exclusion: those who do not prescribe the preparation must surely agree that its exclusion is inconsistent and the reason for it obscure.—I am, etc.,

London, W.1. PETER R. BATESON.

SIR,—Space forbids the detailed criticism of your leading article on the new *National Formulary* (*Journal,* February 12, p. 402) which I—and no doubt others—would like to make. I will therefore only say about "bottles of medicine" that they allow a much more flexible control of dosage than do tablets, and that the modern tendency to tablets involves tablets of an ever-increasing multiplicity of sizes and combinations which is becoming an overpowering burden to the prescriber and an added expense to the State.

To suggest that the *N.F.* is "slavishly following customs which may be ill-informed" because it reinserts the ammonia and senega mixture is, I submit, prejudice rather than therapeutics. Unfortunately pharmacology is largely based on normal animals and defines an expectorant as a substance that increases the bronchial secretion. This is difficult to determine and few substances seem to do it. But the physician is concerned with inflamed surfaces, and is not worried too much about the amount of secretion but whether or not his mixture eases the patient ; and at least three generations of doctors and patients have experienced the striking relief that this mixture will give in the early stages of a hard cough. This stage may seldom be seen in hospital—and anyhow few pharmacologists nowadays would be willing to try the mixture—but in general practice we do see such cases and also the relief afforded. Incidentally, the omission of the monograph on expectorants does not "reflect the contemporary opinion that they are unnecessary and ineffectual" but was due to quite other causes.

Academic pharmacologists may well criticize some other features, but they should remember that the *Formulary* is not a textbook ; and they might even welcome its apparent vagaries if they remembered the danger which both practical and academic medicine run of being cribbed, cabined, and

confined in a national health service which is potentially authoritarian. There is a strong feeling among practitioners that the *Formulary* is in some way an attempt to direct their prescribing, and it is essential to demonstrate that it is, and indeed only can be, merely a help, if the increasing drift to proprietary preparations is to be arrested. Actually your leading article suggests that the writer's mind is not far removed from a dictator's in his concluding remarks on "the development of sensible, honest, logical, and economical prescribing habits," for his first two epithets unconsciously (I hope) ascribe mental perversity and moral obliquity to those who do not agree with him. We do not expect this attitude in the *British Medical Journal*.

I think that those who remember the story of the ergot alkaloids will agree that "contemporary opinion" may be at fault and G.P. experience not quite negligible. At least the compilers tried to hold the scales even. The final result inevitably represents the pressures as well as "the dispensing habits of its country of origin," but I hope it also reflects the whole-hearted efforts of us all to make it as worthy and helpful a volume as we could. I should like to say what a privilege and honour I felt it to be one of the B.M.A. representatives on the revision committee, and what a pleasure and education I found it to work with so many people with whom I often disagreed but from whom I also learned so much. I trust that the doctors of the country will give the *Formulary* a more cordial welcome than your leading article, and, above all, that, in spite of its many shortcomings, they will use as much of it as they can and find the value of some formulae which they have not used hitherto.—I am, etc.,

Winsford, Cheshire. W. N. LEAK.

Laryngeal Paralysis Following Thyroidectomy

SIR,—The recent medico-legal case of complete laryngeal paralysis following thyroidectomy (*Journal*, February 12, p. 426) should stress the essential pre-operative examination which is often neglected—namely, laryngoscopy. This simple procedure would prevent irreparable damage.

It is not uncommon in cases of thyrotoxicosis for a symptomless unilateral abductor laryngeal paralysis to be present. It only requires damage to the other side to make the paralysis complete. A preliminary laryngoscopy and an awareness of a unilateral paralysis would allow for an alternative treatment to be adopted.—I am, etc.,

London, E.11. C. J. SCOTT.

Fatal Pulmonary Embolism in Psychiatric Patient

SIR,—I was interested to see the memorandum on pulmonary embolism in a psychiatric patient by Dr. Donald Blair (*Journal*, February 5, p. 335), as it immediately reminded me of a similar case which recently came under my care.

The patient was a woman of some 40 years, suffering from severe endogenous depression of sudden onset. After being kept in bed for a few days on fairly heavy sedation, and while awaiting air evacuation to the U.K., she was commenced on a course of unmodified E.C.T. A few hours after the second session she complained of pleuritic pain in the left side of her chest, and over the next few days developed a haemorrhagic pleural effusion associated with persistent blood-staining of the sputum and a low-grade pyrexia. Following aspiration the remaining fluid absorbed quite quickly and her chest *x*-ray revealed no evidence of rib fracture. There was at no time any evidence of phlebothrombosis in the legs, and her heart was normal.

I concluded at the time that her pulmonary infarct was probably caused by a pulmonary arteriolar thrombosis consequent upon the period of anoxia and disturbed pulmonary blood flow at the time of her E.C.T. As Dr. Blair points out, small segments of calf-vein thrombosis can be notoriously difficult to detect clinically, and it may well be that her infarct too was embolic in origin. Certainly the immobility in bed of some of these heavily sedated patients combined perhaps with some degree of dehydration, in the absence of energetic tube-feeding, must predispose to venous thrombosis in the legs. I would be interested to learn of any similar cases to the one described above, particularly with regard to whether the incident followed E.C.T. or not.—I am, etc.,

Luton. P. G. JACKSON.

Premedication of Children for Tonsillectomy

SIR,—In his letter (*Journal*, January 29, p. 285) Dr. W. N. Rollason describes a variety of premedications and anaesthetic techniques for this operation. I am surprised he found method (4) (chloral, atropine, ethyl chloride, and ether) too time-consuming. Using atropine only, followed by nitrous oxide, oxygen, and ethyl chloride administered from the Y-piece attachment to the Boyle's machine as already described,[1 2] about 10 cases can be done in an hour.

While "a trace of trichlorethylene" is a valuable adjunct to nitrous oxide in operations *not requiring relaxation*, it would appear to be unsuitable here on account of its inability to relax the jaw and the pillars of the fauces (as is essential for a clean guillotine tonsillectomy) without producing tachypnoea in the child.[3 4] Perhaps the secret lies in the phrase "correctly administered from a McKesson machine."—I am, etc.,

Aberdeen. JAMES B. STIRLING.

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Toxicity of D.A.D.P.S.

SIR,—Since the reports of Esteves and Brandao in 1950[1] and of Cornbleet in 1951,[2] di-amino-diphenyl sulphone (D.A.D.P.S.) has been widely used for the control of dermatitis herpetiformis, and it is generally agreed that toxic symptoms are infrequent and mild. The following brief case history suggests, however, that occasionally severe and rapidly developing toxic effects may occur, with the small doses usually employed.

A rather frail woman, aged 68, developed blisters in the mouth. Several months later there were grouped irritable papules on the forearms, with occasional small blisters. Biopsy showed a sub-epidermal blister containing polymorphs with an inflammatory cell infiltrate in the underlying corium. No other physical abnormality was found. She was given D.A.D.P.S. 50 mg. daily. When seen one week later she complained that the tablets had made her feel ill, with nausea and some vomiting. For two days she had become yellow, with dark urine and light-coloured stools. She had only taken the tablets for four days. On examination she was not jaundiced and there were no abnormal physical signs apart from the blisters. Hb, 65%; R.B.C., 3,000,000; C.I., 1; M.C.D., 7.9; W.B.C., 5,000; neutrophils, 67%; eosinophils, 9%; basophils, 2%; leucocytes, 20%; monocytes, 2%; total plasma protein, 4.5 g. per 100 ml.; albumin, 3.8 g. per 100 ml.; globulin, 0.7 g. per 100 ml.; serum bilirubin, 0.4 mg. per 100 ml. One week later these tests showed: Hb, 75%; R.B.C., 3,800,000; reticulocytes, 1/100 red cells; W.B.C., 6,000; polymorphs, 56%; leucocytes, 34%; plasma protein, 5.7 g. per 100 ml.; albumin, 4.4 g. per 100 ml.; globulin, 1.3 g. per 100 ml. Eight weeks previous to this episode the blood count was: Hb, 95%; M.C.D., 7.3; W.B.C., 5,000; polymorphs, 60%; leucocytes, 34%; eosinophils, 3%; monocytes, 2%; basophils 1%.

It seems probable that in this case D.A.D.P.S. in a dose of 50 mg. daily for four days produced a rapidly developing anaemia and also hepatitis. The evidence is not, of course, conclusive, but strongly suggests this. Haemolytic anaemia is a well-known complication of sulphone therapy, but usually develops gradually in the first weeks of treatment. Allergic hepatitis and exfoliative dermatitis are described occurring during the first nine weeks of treatment.[3] Previous sensitization with D.A.D.P.S. or sulphonamides might result in the onset of allergic hepatitis or aplastic anaemia at the beginning of D.A.D.P.S. treatment, but as far as is known she had never been given these drugs.—I am, etc.,

London, W.2. R. G. HOWELL.

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Dyspareunia Clinic

SIR,—We were glad to see Mr. R. Christie Brown's reference (*Journal*, January 8, p. 106) to a new clinic which is to deal with dyspareunia cases. Up to the present University College Hospital is, we believe, the only teaching hospital to provide special sessions for work of this sort. Cases of introital spasm, leading to dyspareunia or to total unconsummation, are common and can be tedious to treat. Invariably the patients are anxious, and their resulting sexual maladjustments and infertility require time for suitable management and advice. At such sessions the methods used are mainly those of persuasion, whereby the patient is shown how to insert graduated dilators and how to ensure, by alterations of posture, the optimum relaxation of the levator spasm. Such tuition should, as correspondents have pointed out, be given in a normal out-patients session, provided there is leisure and opportunity for weekly return visits. But surely this could be true only of non-teaching hospitals? It would hardly be possible for a nervous woman to spend several minutes learning to insert vaginal dilators in front of a group of students. In practice, therefore, the case must be passed on to a house-surgeon, a delegation that, as another correspondent observes (*Journal*, February 12, p. 415), is a most unsuitable arrangement.

At University College Hospital the cases received are inter-departmental, being referred from the sub-fertility, gynaecological, and obstetric clinics. There are seldom less than one or two new cases at the weekly session, and generally three or four old ones. One student only is accepted for tuition at a time, and privacy from nursing staff, and so on, is assured. Patients who reach this clinic have frequently drifted on from other hospitals where no such facilities have existed. Some of them have delayed renewing their efforts until it is already too late for childbearing or until their marriages are breaking up. We therefore welcome this new clinic under the auspices of the Family Planning Association, and we believe that some hospitals and general practitioners will be glad of its services. We understand that patients are attended by a consulting gynaecological surgeon with special experience of psychoneurotic disorders.—We are, etc.,

W. C. W. NIXON.
JOAN MALLESON.

London, W.C.1.

POINTS FROM LETTERS

Negative Tuberculin Test and Positive X-ray

Dr. R. CHAKRAVERTY (Yeovil) writes: The observations of Dr. R. Stevenson Doig (*Journal*, January 22, p. 225) are very interesting, warranting careful study. . . . His suggestion that an individual who had an infection and then lost sensitivity (allergy) later, and yet showed *x*-ray evidence of a lesion following the infection, would react more markedly to B.C.G. vaccination than a totally non-infected one is a very problematical one and cannot be so dogmatically answered. Schwabaker and Wilson (*J. Path. Bact.*, 1938, **46**, 535) and Wells and Brook (*Brit. J. exp. Path.*, 1940, **21**, 104) experimentally reproduced this condition and found that the return of hypersensitivity (allergy) was not accelerated, but on the contrary markedly delayed and suppressed. It would be very interesting to know further investigation results.

Gelatin-walled Suppositories

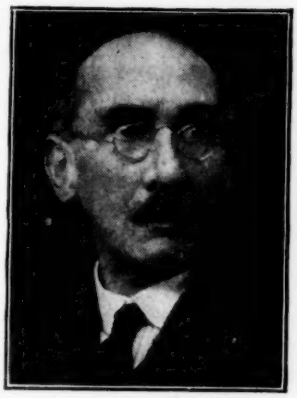
Dr. R. F. MILLER (London, W.1) writes: It has always seemed strange to me why manufacturers do not make gelatin-walled capsules containing glycerin, rather than the solid and almost insoluble product which goes under the name of glyc. suppos. *B.P.* The latter can be retained for as long as 10 minutes or more without any obvious reduction in size or appreciable action on the lower bowel. A thin-walled capsule on the other hand would dissolve in no time, scattering its contents as effectively as a glycerin syringe. I have asked several chemists if such a suppository is available, and they say no. It would be particularly useful with babies, where a quick action is desirable before they can "push it out." It need not be made with a soft or semi-soft wall. Indeed, a rigid capsule, like the oral variety, would probably lend itself to easier self-insertion.

Obituary

Sir CHARLES J. MARTIN, C.M.G., D.Sc., LL.D. D.C.L., M.B., F.R.C.P., F.R.S.

A long career in medical research and medical education, spent on two continents and reaching high distinction in both, is closed with the death on February 15 of Sir Charles Martin. He was 89 years of age.

For more than a quarter of a century Martin was director of the Lister Institute of Preventive Medicine in London, but before he took up that appointment he had already, in his twenties and thirties, built up a reputation in Australia, where his name is still acclaimed after half a century as one of the founders of Australian medical research. When in 1952 the Jubilee of the Australian Commonwealth was celebrated, Mr. R. G. Menzies, the Prime Minister, sent Martin, then 86 years of age, a letter extending the greetings and good wishes of the medical research workers throughout the Commonwealth and announcing that the National Health and Medical Research Council of Australia had created two Fellowships in medical science named after him, to be awarded periodically to young Australians in order to give them overseas experience. The same Council addressed to him a memorial letter signed by all its members which said, "Your work and teaching in Australian institutions laid a solid foundation of research in this country and your example and encouragement stimulated its progress through its formative years. Your inspiration still permeates its whole fabric, and you are remembered by Australian workers as one of their most distinguished masters."



[Press Portrait Bureau

Charles James Martin was born in London in 1866 and was privately educated before entering St. Thomas's Hospital, where he won a scholarship in his second year. Later he was exhibitioner, gold medallist and university scholar in physiology, demonstrator in biology and physiology, and lecturer in comparative anatomy at King's College. He also studied at the University of Leipzig, where he was the devoted pupil of Karl Ludwig, the famous German physiologist. He had among his friends at that time two great physiologists, William Bayliss, who was at University College, and Ernest Starling, who was at Guy's, both of them born in the same year as Martin himself. He qualified in medicine in 1889, graduating M.B. in the following year, and in 1891 he went out to Sydney as successor to Almroth Wright, who had been demonstrator of physiology at the University. He remained in that post until 1887, when he became lecturer in physiology at the University of Melbourne, being appointed professor four years later.

The period was a formative one, both in Martin's career and in Australian medicine. Not only did he help to lay the foundation of Australian medical research, but he had great influence on medical education in the

Commonwealth. As professor of physiology at Melbourne he worked in company with that fine group of teachers, Halford the anatomist, Lambert the physicist, Baldwin Spencer the anthropologist, and others. Martin was a man who had not only great skill in medical research but that intuition which makes all the difference between pedestrian accomplishment and genius. He had also the gift, invaluable in those early pioneer days in Australia, of making laboratory equipment out of all sorts of odd materials. Even in his old age he described his chief recreation as "tinkering." Moreover he had the gift of stimulating research workers, a faculty which came into full play in later years when he was director of the Lister Institute.

Many medical men who received their training in Australia and afterwards rose to eminence in medicine in Great Britain—men like Sir Thomas Dunhill, Sir Howard Florey, Sir Hamilton Fairley, Professor G. R. Cameron, the late Sir Hugh Cairns, and others—were either Martin's pupils or the product of the system of medical education in the Commonwealth which he was active in helping to form. Indeed, from one point of view Australia regarded the position with some dismay. Here she was training at her new universities men whose talents found fulfilment in the mother country. Martin had been heard to declare that the quality of the medical students he met on the other side of the world was higher than at home: he found intellectual adventure more congenial to them and the experimental method of approach more natural.

In 1903, when he was 37 years of age, Martin returned to London to take charge of the Lister Institute of Preventive Medicine. This Institute, of which Lister himself was one of the founders in 1891, was modelled on the Pasteur Institute in Paris, and from year to year it has carried out mostly long-term researches in various fields. Among the problems of medical research which owed much to Martin's stimulus and interest were plague, caisson disease, infantile diarrhoea, the chemistry and metabolism of fat, adrenaline, fermentation, calcification of bone, and the role of vitamins in nutrition. In problems of nutrition and also of immunology he still continued to take an active interest in spite of the claims made upon him as director of the Institute and also as professor of experimental pathology in the University of London—a post to which he was appointed in 1912. From 1904 to 1907 he acted as chairman of the War Office committee on anti-typhoid inoculation; later he was a member of the advisory committee for the investigation of plague in India. This committee, whose work extended over eight years, was appointed jointly by the India Office, the Royal Society, and the Lister Institute. Martin himself went to India on behalf of the committee to organize the investigation.

During all this time his contacts with Australia continued, especially through the constant flow of Australian graduates to the Lister Institute. He had himself two further experiences of Australia. One of these was in the first world war, when he served, with the rank of lieutenant-colonel, in the Australian Army Medical Corps. He was at Gallipoli, where he organized laboratory services and resolved difficulties which had arisen in the field of amoebic and bacillary dysentery and the different typhoid fevers. He served also in Egypt, Palestine, and France, and in his service in France he superintended laboratories in Rouen. He was twice mentioned in dispatches and received the C.M.G. in 1919. In the 'thirties, immediately after his retirement from the Lister Institute, he visited Australia at the request of the Australian Government to assist in some problems closely connected with its health and economy, including work on myxomatosis in rabbits. From 1931 to 1933 he was chief of the Division of Animal Nutrition of the Australian Council for Scientific and Industrial Research, and during the same period Adelaide—his third Australian university—welcomed him with open arms to its research institute as professor of biochemistry and general physiology.

Sir Charles Martin, who was elected F.R.S. in 1901, received the Royal Medal of the Royal Society in 1923, and was appointed a member of the Medical Research Council in 1926. He was a Doctor of Science of London and Melbourne and held honorary doctorates of the universities of Sheffield, Edinburgh, Durham, and Trinity College, Dublin, and the honorary M.A. of Cambridge. He was knighted in 1927. Over the course of years he gave valuable advice and help to the B.M.A. At the Annual Meeting in 1908 he was president of the Section of Pathology, and two years later he was president of the Section of Bacteriology. He was first elected to Council in 1904 and served off and on until 1916. After the first world war he was a member of several committees, including the Science, Arrangements, and Postgraduate Committees.

Sir Charles Martin married Edythe, daughter of Alfred Cross, of Hastings, and had one daughter. His wife died in March, 1954, at the age of 94, after 63 years of happy married life.

We are indebted to Sir ALAN DRURY for the following appreciation: Although I had known Sir Charles Martin as a scientist for many years, it was when I came to direct the institute he had created and to learn its intimate history that I realized what a rare personality he had. The development of the Lister Institute during his directorship, both in the quality of its science and in the men it produced, was remarkable, and was due entirely to his inspiring and enthusiastic leadership.

Martin was essentially the man of the laboratory. Within the laboratory he was supremely competent, and he found his happiness in making the "bits and pieces" for his or other workers' experiments and in carrying out the experiment himself. He had an intense and wide curiosity, an uncanny knack of appreciating the essence of a problem and the lines upon which its solution might be possible. Widely read and with an excellent memory, he was able to help many colleagues, and he could give completely of himself, because self-advancement did not appeal to him. A severe critic, he demanded high standards of performance and would not tolerate slipshod work.

Whimsical in word and manner, humble and straightforward, there was no one who would hesitate to seek his help and advice. It is easy to see why he was so successful a director and why he was so beloved. Living to a great age, he kept his scientific curiosity to the end. He followed the careers of those he had trained and helped and kept abreast of the literature. He seemed able even to regard the disabilities of his advancing years as scientific problems, so that when he spoke of them one felt he was still within the laboratory. There was nothing he enjoyed more than the visits of his colleagues. One can only hope that he appreciated that they came, not from a sense of duty, but because they wanted to hear his comments upon their activities, which they knew would still be valuable, and to meet again a man who was so unique and endearing.

Dr. LESLIE J. HARRIS writes: May I be permitted to add my tribute to the many that will be paid to the memory of Sir Charles Martin? It was in his capacity as chairman, from 1935 to 1946, of the committee of the Dunn Nutritional Laboratory that I had the privilege of getting

to know him well, and so of coming to respect, to admire, and to love him. Intellectually, what stood out most was his astonishing width of interest and knowledge, in the most varied fields of medical research. Equally at home in many specialized departments of pathology, physiology, bacteriology, or biochemistry, he had the gift of seeing right into the heart of a problem; and, knowing as he did how the present knowledge had been won, he quickly sensed what gaps still remained to be filled in. He was interested in knowledge for its own sake, and, unlike some lesser men, judged a research finding on its merits alone, not by its authorship. In consequence he was able to recognize talent and originality where others might miss seeing it, and, as a result, had the satisfaction of fostering young and sometimes precarious, research careers—leading in one instance at least to a later Nobel Laureateship. He was never one of those prone to put his own name on the title of the papers of his assistants and students published from his institute. On the contrary, it was an open secret that during the years that he was director of the Lister Institute much of the now classical work appearing under other names was really suggested, inspired, and directed—sometimes even down to the smallest technical details—by "Sir Charles," who took a pride in being a competent technician and handyman.

His scientific integrity was marked by a robust sense of right and wrong and fair dealing, combined with practical common sense. He was prepared, in no uncertain voice when occasion demanded, to stand up against established authority, when he knew that authority to be in the wrong; and his courageous determination more than once won the day. To his junior colleagues and to his friends he could at times be blunt and outspoken to a degree, but his direct speech never caused resentment, and it was in fact appreciated because one recognized the kindly heart behind it, and one was warmed by the friendly, welcoming smile always lurking below. Although in his own tastes simple to a degree, he could prove himself a man of the world in dealing with officialdom. He himself had the gift of handling men, and of dealing effectively with committees and organizations: indeed, one of his maxims was that people who failed to rub shoulders with their contemporaries had not succeeded in learning one of the elementary "techniques" of their trade. Another of his maxims was that it is useless to appeal to reason where a person's emotions have become involved. Up to the end Sir Charles retained both his charm and his penetrating intellectual faculty; and it was an experience to hear him, at the end of the ninth decade of his life, giving his stimulating comments on some future scientific developments which he foreshadowed after reading a paper that had just appeared in the current issue of a scientific journal.

PHILIP TURNER, M.S., F.R.C.S.

Mr. Philip Turner, consulting surgeon to Guy's Hospital, died on February 16 at St. Mary Abbots Hospital. He was 81 years of age.

Philip Turner was born in Kensington on December 27, 1873. Before studying medicine he graduated B.Sc., with honours in zoology, at University College, London. He then went on to Guy's Hospital, qualifying in 1897. Two years later he took the M.B., and in 1901 he became F.R.C.S. and proceeded to the degree of M.S. At Guy's he won the Treasurer's gold medal in clinical surgery, and his early appointments there included those of medical registrar from 1902 to 1903, and demonstrator in anatomy from 1903 to 1908. Meanwhile he had obtained the appointment of assistant surgeon at the Belgrave Hospital for Children, but he relinquished this in 1908 on his election to the staff at Guy's as assistant surgeon and demonstrator of operative surgery. For several years he was in charge of the ear department. Mr. Turner was not one to seek the limelight, but his excellent qualities earned for him a solid and enduring reputation as a general surgeon, and among other hospitals to which he was attached were the Eltham and Hornsey Cottage Hospitals and the Surrey Dispensary. He had retired from the active staff of Guy's before the second world war, but in 1940 he joined the E.M.S., and for ten years thereafter worked as a surgeon at Joyce Green Hospital, Dartford, where his vitality and keenness will be long remembered.

He wrote numerous articles on surgical subjects for the medical journals, and several books. In 1908 he had two books published on the subject of osteology, *The Pocket Osteology* and *Aids to Osteology*, and he described some of his own contributions to operative surgery in *Inguinal Hernia, the Imperfectly Descended Testicle, and Varicocele* (1919). With Mr. R. P. Rowlands he edited *The Operations of Surgery*, and he contributed to Latham and English's *System of Treatment* and Choyce's *System of Surgery*. In 1908 he married Miss Helen B. Lambert, who was formerly a sister at Guy's and during the first world war matron of the Central Red Cross Workrooms at the Royal Academy. She died in 1932.

We are indebted to Sir HENEAGE OGILVIE for the following appreciation: Philip Turner will be remembered with affection by all who have passed through Guy's in the last 50 years. To the world of medicine as a whole he was a little-known figure, for he was quiet and shy in his manner, dressed formally, entertained little, and made surgery and his hospital his life. With R. P. Rowlands he edited the several editions of Jacobson's *Operations of Surgery*, and was largely responsible, after Rowlands's death, for the eighth edition. He himself wrote on hernia and scrotal conditions, and described the operation of trans-scrotal fixation of the undescended testis that bears his name and that remains the best method to-day.

As an operator he was scrupulous rather than spectacular. Whatever he did he did gently and bloodlessly, displaying a craftsman's hands and an anatomist's knowledge of topography. At a time when operating by the clock was fashionable and dramatic surgery was more admired than it is to-day, he taught to many generations the value of careful technique.

When I first knew him he was assistant surgeon to Sir Alfred Fripp, and his gentle, almost apologetic manner stood in marked contrast to the masterful personality and easy address of "The Baron." He grew in stature year by year as his sterling worth came to be appreciated by successive generations. Having retired from the staff when at the height of his powers, he was called back into harness at the outbreak of the second world war and given the post of chief surgeon at a large E.M.S. hospital in the Guy's sector. He entered into this assignment with a boyish enthusiasm, and in his new duties developed a new personality, a power of leadership, and social gifts that had hitherto lain dormant. I saw him last when he took the chair at the Guy's Biennial Dinner in October, 1954. It was moving to see the universal affection in which "Philip" was held, and the pride with which he looked round that great gathering of Guy's men, most of whom had been his pupils.

The death took place on February 19, within nine days of his 81st birthday, of Dr. EDGAR F. CYRIAX, manipulative surgeon and physiotherapist, apostle of physical fitness, and one of the earliest and most ardent exponents in this country of Swedish gymnastics. Edgar Ferdinand Cyriax was born in London and educated at University College School and University College, afterwards taking his medical training in Edinburgh, where he graduated in 1898, proceeding to the Edinburgh M.D. in 1901. He was attracted to the Swedish methods and became a graduate of the Central Gymnastic Institute of Stockholm. One of his earliest monographs, published in 1903, was on the elements of the manipulative treatment practised there by the director, Henrik Kellgren,

whose daughter, herself a medical woman, Dr. Cyriax married. During the first world war he was visiting physician to the Swedish War Hospital, and afterwards, from 1919, visiting physician to the British Hospital for Functional Mental and Nervous Disorders, Camden Town. Until his retirement only a short time ago he continued in private consulting practice, describing himself as a specialist in mechano-therapeutics. During his lifetime he wrote a number of papers on subjects connected with physical medicine: one, entitled "Minor Displacements of the Vertebrae and Ilia," was published in the *Practitioner* in 1916, and another, about the differences between blood-pressure readings in the two arms, in the *Quarterly Journal of Medicine*. Dr. Cyriax achieved a great reputation in the field of sport. He was the grand old man of Rugby fives, a game which he had learned at University College School 70 years ago, and which he continued to play well into his old age. He did much to popularize the game in public schools. His prowess in physical achievement became something of a legend. He disdained the car—"You just sit there and go flabby"—and cycled between his Welbeck Street surgery and his Hampstead home. Similarly he preferred the staircase to the lift. He hardly ever wore hat, overcoat, or gloves even in winter, and he boasted of his cold bath every morning. He was a Knight of the Royal Swedish Order of Vasa (First Class) and a member of the French and Belgian Societies of Physiotherapy, and he had been a member of the British Medical Association for more than 50 years. Dr. Cyriax is survived by his widow and by his son, Dr. James Cyriax, and his daughter, Dr. A. V. K. Cyriax.

A memorial service for the late Sir EDWARD MELLANBY will be held at St. Martin-in-the-Fields at 11.30 a.m. on Thursday, March 17.

Medico-Legal

VACCINATION CLAIM WON

On February 14 Dr. Brian Quinn, of Mytholmroyd, near Halifax, successfully claimed for £62 15s. against Halifax Corporation Health Department in respect of 251 vaccinations and the compiling of records while house-physician at St. John's Hospital, Halifax, during 1953. The judge granted a stay of execution for 14 days in case of an appeal.

Dr. Quinn's case was that in March, 1953, there was a smallpox scare in the Halifax area and many vaccinations were carried out. The corporation paid a total of £445 to general practitioners who did vaccinations and submitted records, but it had declined to pay any hospital doctors who did the same work. Dr. Quinn contended there was no possible distinction between hospital doctors and general practitioners who carried out vaccination work. Questions of fact which arose were: Did the local authority in fact make arrangements with Dr. Quinn through the medium of the senior medical officer, and was there a request expressed or implied that a record should be completed and submitted to the local authority?

In March, 1953, there were two suspected cases of smallpox—one at Halifax General Hospital and another at St. John's Hospital. Conferences were held between the hospital authorities and the medical officer of health for Halifax, and at all these conferences the M.O.H. or his assistant was present. Ultimately instructions were given by the acting M.O.H. to the senior medical officer at St. John's Hospital that vaccinations should be carried out on anyone likely to have come in contact with a suspected smallpox case. Dr. Quinn was told to get on with the work, vaccine was supplied free of charge, and record cards were sent.

Dr. Quinn said that he did not regard it as part of his job at the hospital to vaccinate patients and send in record cards.

Mr. R. W. Ranson, group secretary, Halifax Hospitals Management Committee, expressed the view that if any fees were paid they should be retained by the doctor.

The Corporation contended that neither it nor its agents made arrangements with Dr. Quinn. Any action should have been brought by Dr. Quinn's employers, as the arrangements were made with his superior on behalf of the hospital management committee. Vaccination of contacts was one of the incidental duties a doctor might have to do in the course of his ordinary work in the hospital.

Judge Myles Archibald said he found there was the clearest intention by the health department that these doctors should be invited to do the work. He did not think a hospital was the sort of place where one would normally expect this sort of work to be done. It was not part of Dr. Quinn's duty to carry out vaccinations in this sense or to fill in record cards.

The Medical Defence Union instructed Messrs. Hempsons, solicitors, to act for Dr. Quinn.

Medical Notes in Parliament

ETHICS OF CLINICAL INVESTIGATIONS

The conduct of clinical trials in hospitals, and the right of the patient to be informed and to give or withhold his consent, were discussed in the House of Commons on February 16. It was raised by Mr. STEPHEN SWINGLER (Newcastle-under-Lyme, Lab.), and arose out of trials conducted at Bristol Maternity Hospital and reported in the *British Medical Journal*, December 11, 1954, p. 1392.

Mr. Swingler said that, while the community should give to medical scientists and doctors the best possible facilities and conditions for research, medical scientists and doctors should be extremely careful not to use their privileged position to treat human beings as laboratory specimens. He put forward two principles: medical experiments on patients should not be conducted unless there was a chance of patients benefiting; and clinical experiments in hospitals should not be conducted unless the consent of the patients had been freely given, in the knowledge of the nature of the experiments. The doctor should explain to a patient that experimental treatment was necessary, the nature of the experiment, the risks involved, and the benefits that might be obtained or the injury that might result.

In the Bristol case, he said, penicillin was administered to newly born babies for the purely scientific purpose of observing their reaction to penicillin and to establish the properties of the preparations. The penicillin was not required by the babies, and there was no question of its having any beneficial effect on the babies. It had been established by the Minister of Health on inquiry that the consent of the parents was not sought. In his opinion, even if consent had been given, the experiment was ethically dubious. In the opinion of those who conducted this experiment, and of the Minister, there was no possibility of harm being done. But in the same issue of the *Journal* in which the experiment was reported there was a report of a speech by a distinguished doctor to a meeting of the Royal Society of Medicine about the uses and abuses of antibiotics, in which he was reported to have said that a doctor should think twice before prescribing the first-ever dose of penicillin to any patient.

A search of the medical press over the past two or three years had shown him at least half a dozen reported cases of clinical experiments on children in hospitals, not designed to benefit the children in any way, but said to have been carried out merely to test the reaction to certain drugs. That was treating children as guinea-pigs. The Minister had said that judgment could be left to the clinician in charge, but he (Mr. Swingler) would point out that some clinicians allowed their enthusiasm for science to override all moral objections. He would have thought that it was the responsibility of the Minister of Health, in conjunction with the

Ethical Committee of the B.M.A. and the Medical Research Council, to lay down some guiding principles. He urged the Minister to consult with his advisers and with these organizations, to see if some directive or code could be sent to hospitals to prevent and prohibit experiments, especially on children, which were for purely scientific purposes and not designed in any way for the promotion of health. In this way some ethical guidance might be given which would act as a necessary and desirable curb on the enthusiasm for enlarging scientific knowledge.

Major W. J. ANSTRUTHER-GRAY (Berwick and East Lothian, Con.) was concerned that all consideration of the parents appeared to have been overlooked. He quoted extracts from the *Journal* report, and said that he had no doubt the experiment was quite harmless. There was a note at the foot of the article in which a lot of people were thanked. But the parents were not only not thanked, they were not even consulted.

Future to Benefit

Mr. IAIN MACLEOD, Minister of Health, said it was admitted that the consent of the parents should have been asked for. The people responsible, who were of the greatest authority and competence, regretted very much—as he did—that that was not done. What the House was discussing was whether such experiments were proper, and whether any action should be taken by the Minister in these matters. He disagreed with Mr. Swingler's proposition that it would be wrong and unethical for any clinical investigation to be carried out which would not immediately benefit the person concerned. If it was to add to future knowledge he did not see how that could be so. The reward to those who tried to catch the common cold at the Salisbury research unit was not that they would derive direct benefit themselves, but that the general pool of knowledge might be increased and others helped in the future. The answer to Mr. Swingler, therefore, was that babies yet unborn might benefit from this continued thrusting forward to new frontiers.

There were two propositions with which he thought most of the House would agree. First, there was bound to be clinical investigation and experiment. If that were not so, knowledge of surgery and medicine would not have changed over the centuries. Second, only the clinician in charge could say what was right and proper and what safeguards were needed in the action he took. Mr. Swingler had asked, in questions on February 14, that before further clinical experiments on children were undertaken the nature of such experiments should be reported to the Ministry of Health so that the medical staff of the Ministry could ensure that there were adequate safeguards against harmful effects; and also that the Minister should issue a directive to hospital management committees on the ethical principles involved. That was in his (Mr. Macleod's) view a wrong conception of the duty of the Minister of Health. He thought it would be wholly improper for him to try to lay down what ethical and medical principles should govern the conduct of professional men in the work they undertook at hospitals.

In this instance there was undertaken an experiment which all those concerned, who were of the highest capability, were quite certain was completely harmless. If a small child of his, or a child of any age, was in hospital, and he was told by people of the standing, for example, of professor of medicine and child health at the university concerned, "We are interested to know the effects of a perfectly safe clinical investigation; it may very well be that we can learn from what is done, and as a result can drive still lower the infant mortality rate," he would be more than ready to give his consent.

The common sense of the matter was that where a clinician intended to undertake an investigation which was so novel as to amount to an experiment he would be wise to seek consent from the patient or parent for what was proposed. But he was absolutely convinced that it would be quite wrong for a Minister of Health to issue directives on a matter that was essentially one of medical ethics to those concerned. He was sure it was best to leave the matter to the profession, and not to have a lay Minister interfering in a matter that was very precious to those professionally concerned.

Some Guidance Needed

Mr. SWINGLER said he appreciated why the Minister should resist the idea that he should himself go into this matter and issue a directive. But in view of the complexity of the situation, did he not think it was the duty and responsibility of the heads of the medical profession to give some ethical guidance? As it had been brought to his attention that there were cases where, for example, consent had not been obtained, and where experiments were being conducted which had nothing to do with actual treatment, would he not use his good offices to ask the heads of the medical profession to give some guidance on that?

Mr. MACLEOD said that was a very different matter and one with which he was in some sympathy. If he had the slightest reason to believe that the position was not fully understood, then he would informally—and it could only be informally in a matter like this—draw the attention of those responsible to what had been said. The Medical Research Council sent out a confidential memorandum rather on those lines. If he had any reason to believe that the position was not completely clear, and that it was desirable for these things to be drawn to the attention of those responsible, then of course he would not object at all to what he might call an informal notification from himself. Of one thing he was clear: no directive must come from the Ministry of Health on a matter of this delicacy.

The discussion was part of the debate on a Supplementary Estimate for the National Health Service, which was agreed to.

HEALTH SERVICE COSTS

The supplementary estimate of £4,848,000 for the Health Service (*Supplement*, February 19, p. 56) was presented to the House of Commons on February 16 by Miss PAT HORNSBY-SMITH, the Parliamentary Secretary. She pointed out that in spite of the stricter basis on which the main estimates had been prepared, in accordance with the recommendations of the Public Accounts Committee, the net additional amount asked for was only slightly over 1% of the original sum. For a service which covered nearly 3,000 hospitals, 20,000 doctors, 10,000 dentists, 8,000 ophthalmic medical practitioners and opticians, and 15,000 chemists and suppliers of appliances the smallness of the margin was very creditable. The total sum asked for was made up of various increases which amounted to £8,562,000, reduced to the net figure by savings.

The increase for hospital maintenance accounted for £2,608,000, which included increases in pay totalling £1,200,000, additional to the £1,000,000 in the original estimates; increases in costs which accounted for £900,000; and £500,000 to meet expenditure which it had been estimated would be met by running down costs. Last year there was an increase of 8,000 in the daily average of occupied beds, of 125,000 in the number of new outpatients, and of 270,000 in casualty attendances. An additional £2,133,000 for the pharmaceutical services was due mainly to an increase in the average cost per prescription and in the number dispensed, and to a wider use of the newer and often more expensive drugs and preparations. Doctors were continually being kept cost-conscious in various ways, most recently through the introduction of arrangements by which a doctor could compare the cost of his own prescribing with that of his colleagues. Discussions between the Ministry and the manufacturers on price investigations had resulted in a number of reductions, and prescription had been kept reasonably stable over the past three years in spite of the almost continuous introduction of new drugs. The average cost in 1952–3 and in

1953–4 was 4s. 1d., and this year was expected to be about 4s. 2¼d., and the increase in the number was expected to be about 4,500,000. The bad summer last year produced a higher incidence of prescriptions than was normal, and the July figure was the highest on record for that month.

The estimated increase in expenditure on the supplementary ophthalmic and general dental services was also due to increased demand.

Pharmaceutical Costs Debated

Mr. H. A. MARQUAND (Middlesbrough, East, Lab.) commented that the largest proportionate increases were in the services provided by the executive councils—pharmaceutical, dental, and ophthalmic—on which charges to the public had been imposed. As there had been no epidemics since last May it looked as if the charges were less of a deterrent than they had been. A fortunate aspect of the increases for dental and ophthalmic treatment was that there was no suggestion of any increase in cost. The pharmaceutical service, however, showed an increase in both demand and cost, and that deserved more scrutiny. Why was the cost still going up?

Mr. IAIN MACLEOD, Minister of Health, stated that since the Estimates were prepared it had been decided to make the two most expensive drugs, aureomycin and terramycin, freely prescribable. The fact that they could now be prescribed on Form E.C.10 would be a major factor in the increased amount for which the House was being asked.

Sir HUGH LINSTEAD (Putney, Con.) said that the increased cost of the pharmaceutical service was basically due to the fact that medicine was advancing very rapidly, and that new and inevitably more expensive drugs were replacing the traditional and cheaper drugs. These generally reached the market in the form of proprietary medicines, and there was a heavy development and research bill attached to them. In 1950 18% of prescriptions were proprietary; in 1953 the proportion was 27% and in 1954 29%.

Of the report of the working party into hospital pharmaceutical services of which he was chairman, he said there were substantial economies still to be secured in costs, but they would be secured only in so far as the chief pharmacist in each hospital was a person of substantial scientific knowledge, whose advice was listened to by the consultants and medical staff.

Mr. MACLEOD, answering the debate, said that the inevitable concentration on what was wrong in Parliamentary debates and questions did not give an accurate picture of what was happening in this great service. It was worth remembering that since 1948 the number of beds available, the number staffed, and the number occupied, and the number of out-patients, had all gone up every year. There was a very great deal of progress against which the difficulties must be looked at. The general investigation into the secondary manufacture and compounding of drugs had been completed, and they had stated a preliminary view that there was no evidence to show that excessive profits were being made. On basic drugs they were still considering the accountants' report.

There had been a general downward tendency in price of proprietary preparations, and he had no reason to suppose that the investigations were the only, if indeed they were the main, reason for the reductions. Although there were preparations unworthy of being sold under the Health Service, the industry had made a wonderful advance in recent years. It had an export trade of great importance, and research was absolutely vital to it.

Vaccine Tests on Children

Mr. JOHN RANKIN (Glasgow, Tradeston, Lab.) asked the Secretary of State for Scotland if he was aware that 600 children belonging to the Orphan Homes of Scotland, Bridge of Weir, Renfrewshire, had been used for the purpose of research into a new antituberculosis vaccine; that this experiment had been going on for the last three years; that now, as a result, a number of the children were suffering from a chronic skin infection; and if he would make a statement on the matter. Commander T. D. GALBRAITH, the Under Secretary, replied on February 15 that in the course of vaccinating these children against tuberculosis it was arranged in the spring of 1951 between the Department of Health and the county council, with the consent and co-operation of the management, to use B.C.G. vaccine for some of the children and an alternative vaccine—the "vole" vaccine—for others. Earlier studies had suggested that vole vaccine was likely to give as good protection with less local reaction, but late skin reactions on the site of the vaccination had been noted in 20 of 280 children who received this vaccine. He was assured that these reactions had been slight and were all clearing up, while the general health of the children had been entirely unaffected.

Medical Man-power Inquiry

The MINISTER OF HEALTH announced on February 21 the composition and terms of reference of the committee to investigate future needs in medical man-power.

The chairman is to be Mr. HENRY WILLINK, Q.C., Vice-Chancellor of Cambridge, and a former Minister of Health, and the members are:

Dr. J. T. Baldwin, Sir Harold Boldero, Sir John Charles, Sir Henry Cohen, Sir Andrew Davidson, Dr. A. B. Davies, Mr. J. P. Dodds, Sir Geoffrey Jefferson, F.R.S., Mr. L. G. K. Starke, Mr. A. B. Taylor, D.Litt.

The terms of reference are:

To estimate, on a long-term basis and with due regard to all relevant considerations, the number of medical practitioners likely to be engaged in all branches of the profession in the future, and the consequential intake of medical students required.

Mr. P. V. Muston, of the Ministry of Health, will be the secretary to the committee.

Mr. Henry Willink (chairman), aged 60, is Master of Magdalen College, Cambridge, and Vice-Chancellor of Cambridge University. He was Minister of Health in the Coalition Government, 1943–5, and chairman of the Royal Commission on Betting, 1949.

Dr. J. T. Baldwin is a general medical practitioner in Midlothian, a member of the Scottish Health Services Council, and a member of the General Medical Services Committee of the B.M.A.

Sir Harold Boldero, aged 65, is a registrar of the Royal College of Physicians and was dean of Middlesex Hospital Medical School. He holds the position of examiner in medicine at the Universities of Oxford, Cambridge, and Birmingham. He is also a member of the North-west Metropolitan Regional Hospital Board.

Sir John Charles, aged 61, has been Chief Medical Officer at the Ministry of Health since 1950. After being medical officer of health at Newcastle during 1932–44, he was appointed a deputy chief medical officer at the Ministry of Health in 1944.

Sir Henry Cohen, aged 55, is professor of medicine at the University of Liverpool. He is also vice-chairman of the Central Health Services Council, and chairman of its Standing Medical Advisory Committee. He has been chairman of several special committees, including those on general practice and the prescribing of proprietary preparations. He is a member of the United Liverpool Teaching Hospitals and Liverpool Regional Hospital Board.

Sir Andrew Davidson, aged 62, was Chief Medical Officer to the Department of Health for Scotland during 1941–54. He is chairman of the Advisory Committee on Medical Research in Scotland and a member of the General Medical Council.

Dr. A. B. Davies is a general medical practitioner in Walsall who has had experience in industrial medicine, and is a member of the General Medical Services Committee of the B.M.A.

Mr. J. P. Dodds, aged 42, is Under Secretary, Health Services Remuneration and Staffing Division, at the Ministry of Health.

Sir Geoffrey Jefferson, F.R.S., aged 68, is emeritus professor of neurosurgery, Manchester University, and consultant adviser in neurosurgery to the Ministry of Health. He is a member of the Medical Research Council and chairman of the Clinical Research Board.

Mr. L. G. K. Starke is a principal actuary in the Government Actuary's Department.

Mr. A. B. Taylor, aged 50, is an assistant secretary in the Health Services Division, Department of Health for Scotland.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **February 5** (No. 5) and corresponding week 1954.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES In Countries and London	1955					1954				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	16	1	8	0		19	2	9	0	
Dysentery	979	61	287	8	6	624	99	199	0	6
Encephalitis, acute	2	0	1	0		3	1	0	0	
Enteric fever:										
Typhoid	8	0	3	0	1	0	0	0	0	
Paratyphoid	7	0	6	0	1	4	0	1	0	
Food-poisoning	137	19		0		88	19		0	
Infective enteritis or diarrhoea under 2 years				11	14				10	14
Measles*	12,729	1295	399	608	136	1,487	19	50	20	240
Meningococcal infection	43	5	17	2	2	33	4	13	0	2
Ophthalmia neonatorum	39	0	7	0		25	0	3	0	
Pneumonia†	1,157	108	380	58	2	826	37	249	10	2
Poliomyelitis, acute:										
Paralytic	9	0	1	0		17	2	3	0	1
Non-paralytic	4	0				4	1			
Puerperal fever§	240	41	14	2		235	33	7	0	
Scarlet fever	791	59	111	62	20	1,015	41	187	36	20
Tuberculosis:										
Respiratory	751	82	137	21		825	103	141	23	
Non-respiratory	109	13	11	3		111	6	20	4	
Whooping-cough	2,213	162	214	79	33	1,984	45	328	46	54

DEATHS In Great Towns	1955					1954				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	1	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	13	0	3	0	0	10	0	2	1	1
Influenza	106	14	6	3	0	41	3	1	0	3
Measles		0	1	0	0		0	0	0	0
Meningococcal infection		1	1				2	0		
Pneumonia	449	81	43	22	11	382	48	27	16	14
Poliomyelitis, acute	3	1			0	2	0			0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	108	20	11	4	7	120	15	27	1	2
Non-respiratory		0	6	1	1		3	3	0	1
Whooping-cough	2	0	0	0	0	2	0	0	0	0
Deaths 0–1 year	273	28	32	11	14	304	36	41	9	20
Deaths (excluding stillbirths)	7,127	1105	724	166	204	7,142	1018	791	149	219
LIVE BIRTHS	7,807	1122	990	221	414	7,399	1052	946	229	315
STILLBIRTHS	198	26	31			202	34	21		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Influenza

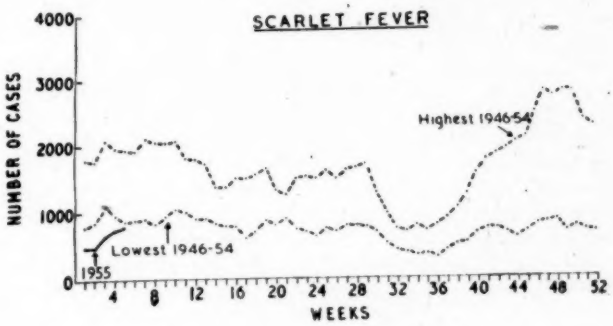
The 84 deaths from influenza in the great towns of England and Wales reported in the week ending February 12 showed a decrease of 22 from the preceding week's figures. This is the third successive week in which the total has fallen. 71 of these 84 deaths were of people aged 55 or over. The outbreak of virus-B influenza is evidently continuing to wane, and there is no evidence that any outbreaks of virus-A influenza are developing.

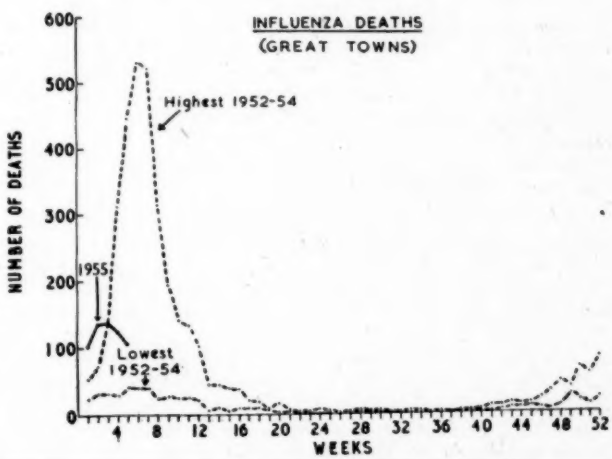
Typhoid in Yorkshire

The cause of the typhoid outbreak at Pickering, in Yorkshire (*Journal*, February 12, page 430), is reported to be contaminated tinned tongue.[1] It was all sold on one day, December 11, 1954. On December 13 an epidemic of an apparently upper respiratory infection, labelled influenza, started in Pickering after (not before, as we previously reported) a similar condition had affected people in surrounding districts. Chloramphenicol was administered to those patients suspected of pulmonary complications, and most of the primary cases subsequently diagnosed as typhoid received a course. The clinical picture was an unusual one —pyrexia, nose-bleeds, headache, and prostration.

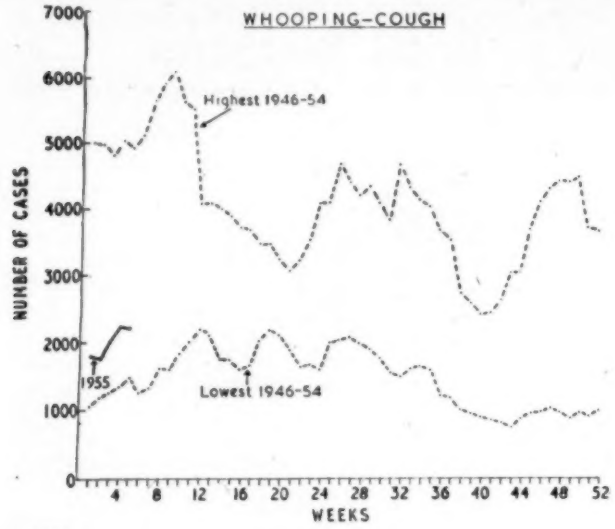
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases (deaths for influenza) of certain diseases notified weekly in England and Wales (great towns for influenza). Highest and lowest figures reported in each week during the nine years 1946–54 (influenza, 1952–4) are shown thus ------, the figures for 1955 thus ———. Except for the curves showing notifications in 1955, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.





[1] *Yorkshire Post*, February 17, 1955.



Infectious Diseases

The rises in the number of notifications of infectious diseases in England and Wales during the week ending February 5 included 2,032 for measles, from 10,697 to 12,729, 301 for dysentery, from 678 to 979, 95 for acute pneumonia from 1,062 to 1,157, and 46 for scarlet fever, from 745 to 791.

The largest increases in the local incidence of measles were 389 in Yorkshire West Riding from 1,464 to 1,853, 280 in Kent, from 286 to 566, 204 in Warwickshire, from 372 to 576, 198 in Nottinghamshire, from 469 to 667, 158 in London, from 1,137 to 1,295, 122 in Durham, from 443 to 565, 104 in Surrey, from 276 to 380, and 101 in Northumberland, from 190 to 291. Only small variations occurred in the local trends of scarlet fever. 2,213 cases of whooping-cough, 24 fewer than in the preceding week, were notified. The largest variation was a rise of 38 in Kent, from 99 to 137. 16 cases of diphtheria were notified, being 7 fewer than in the preceding week. Multiple notifications of diphtheria came from Birmingham C.B. 3, Kingston-upon-Hull C.B. 2, and Liverpool C.B. 2. 13 cases of acute poliomyelitis were notified during the week, and these were 7 fewer for paralytic and 3 fewer for non-paralytic cases than in the preceding week. No multiple cases were reported.

The incidence of dysentery was the largest for 34 weeks. The chief centres of infection were Lancashire 368 (Oldham C.B. 86, Stretford M.B. 61, Blackpool C.B. 59, Manchester C.B. 30, Liverpool C.B. 27, Royton U.D. 15, Chadderton U.D. 14, Huyton-with-Roby U.D. 11), Suffolk 103 (Woodbridge U.D. 78, Blyth R.D. 17), Yorkshire West Riding 67 (Leeds C.B. 26, Rotherham C.B. 17), London 61 (Southwark 23), Norfolk 60 (Norwich C.B. 28, Blofield and Flegg R.D. 15, Forehoe and Henstead R.D. 10), Durham 42 (Lanchester R.D. 23), Glamorganshire 33 (Swansea C.B. 10), Warwickshire 30 (Birmingham C.B. 23), Leicestershire 29 (Leicester C.B. 23), Lincolnshire 28 (Scunthorpe M.B. 27), Yorkshire North Riding 23 (Middlesbrough C.B. 16), and Northumberland 20 (Newcastle-upon-Tyne C.B. 16).

Week Ending February 12

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 746, whooping-cough 2,065, diphtheria 14, measles 18,363, acute pneumonia 1,156, acute poliomyelitis 16, dysentery 1,110, paratyphoid fever 4, and typhoid fever 1.

Medical News

Duke of Edinburgh.—The Royal College of Surgeons of Edinburgh is to confer its Honorary Fellowship on the Duke of Edinburgh on June 20 as part of the College's 450th anniversary celebrations. The last member of the Royal Family to receive the Hon.F.R.C.S.Ed. was the Duke of Cumberland, the younger son of George II. On his return from his victory over the Young Pretender at Culloden Moor in 1746, he was made an honorary freeman of each of the City Crafts of Edinburgh, in gratitude for having come to that part of the kingdom "to maintain, protect, and defend our valuable Constitution of Church and State, most unjustly and unreasonably attacked by the present rebellion."

Sir Godfrey Huggins, C.H., F.R.C.S.—The Queen has approved the conferment of a Viscountcy on Sir GODFREY HUGGINS, Prime Minister of the Federation of Rhodesia and Nyasaland. On February 18, the day the honour was announced, Sir Godfrey broke the Commonwealth record for service as a Prime Minister. He first attained this high office in 1933 as Prime Minister of Southern Rhodesia, a position he held unbroken for 20 years, until in 1953 he became Prime Minister of the newly created Federation of Rhodesia and Nyasaland. The previous record was made by the late Mr. Mackenzie King, who was Prime Minister of Canada for 7,828 days in three separate periods. The son of a doctor, Sir Godfrey Huggins qualified from St. Thomas's Hospital in 1906, and after holding appointments there he became house-physician and ultimately medical superintendent at the Hospital for Sick Children, Great Ormond Street. In 1908 he took his F.R.C.S., but a serious illness three years later compelled him to go abroad. For ten years he was a general practitioner in Salisbury, Southern Rhodesia, but in 1921 he became a consulting surgeon. In the same year he made his first entry into Southern Rhodesian politics. Only last week Sir Godfrey Huggins was in London attending the meeting of Commonwealth Prime Ministers, and while here he found time to go to the Hunterian Festival Dinner at the Royal College of Surgeons (*Journal*, February 19, p. 491). On the day of Sir Godfrey's return to Africa Sir Winston Churchill sent him this message: "I and my colleagues in the United Kingdom wish to send you our warm congratulations and good wishes for the future on your achievement in surpassing all records for the longest tenure of office of a British Prime Minister."

[*Barratt's Photo Press*

National Spastics Society.—The Lord Mayor of London, Alderman SEYMOUR HOWARD, presided at a dinner held at the Mansion House on February 15, when Mrs. CLEMENT ATTLEE and Mr. TED LEATHER, M.P., spoke in aid of the five-year medical research programme of the National Spastics Society. It is hoped that £45,000 will be subscribed to finance this research, which is only one of several projects which the society has in hand, including the setting

up of special schools and local treatment centres for spastic children and adults. Dr. P. E. POLANI, the society's research director, speaking at the dinner, said that the main task of research in this field was to find out the causes of cerebral palsy, but investigations would also be made to assist diagnosis and to assess the potentialities of the handicapped child and the results of treatment.

Royal College of Surgeons in Ireland.—The annual Charter Day dinner was held in the College on February 12, when over two hundred Fellows and guests attended, among them members of the Surgical Travellers' Club. The toast of "The Guests" was proposed by the vice-president, Mr. A. B. CLERY, and was replied to in most felicitous terms by Professor ERIC ASHBY, vice-chancellor of the Queen's University, Belfast, and Sir STANFORD CADE. The toast of "The College" was proposed by Sir HENEAGE OGILVIE, and to this the president, Mr. IAN FRASER, replied.

Liquid Paraffin and Cancer.—One of the studies mentioned in the current annual report of the London School of Hygiene and Tropical Medicine is an analysis of data on the use of purgatives by patients with cancer of the gastro-intestinal tract and by patients with other diseases. These data were collected during the investigations into the aetiology of lung cancer which were published in the *British Medical Journal* (1950, **2**, 739; 1952, **2**, 1271). "The results," says the annual report, "suggest that the use of liquid paraffin may be associated with the development of a small proportion of the cases of cancer of the stomach and of the large bowel."

Dermatology and the G.P.—The reality of the demand from general practitioners for courses in dermatology (see page 534) is attested by figures published last week in the *Cambridge University Reporter* of the attendances at clinical symposia arranged for them at the Cambridge Medical School. Of the eleven symposia, that on dermatology was easily the most popular, 61 practitioners attending it. Next in popularity were those on paediatrics (53), disorders of blood (45), cardiovascular diseases (43), and obstetrics and gynaecology (42). At the bottom of the list were orthopaedics (18) and E.N.T. diseases (12).

French Government Exchange Scholarships.—Under the terms of a reciprocal arrangement with the Centre National de la Recherche Scientifique, the Medical Research Council invites applications from British workers in medical science (excluding clinical medicine) for two scholarships, valued at between 50,000 and 70,000 francs a month and tenable at research institutions in France during the academic year 1955–6. Further details and forms of application from the secretary, Medical Research Council, 38, Old Queen Street, London, S.W.1, with whom applications must be lodged by March 31.

Travelling Fellowships in Ophthalmology and Otology.—The Medical Research Council invites applications for Travelling Fellowships in ophthalmology and otology for the academic year 1955–6 for which special provision has been made by the Alexander Pigott Wernher Memorial Trustees. The Fellowships are intended for medical graduates who are likely to profit by a period of work at a centre abroad before taking up positions for higher teaching and research. The rate of payment is £650 per annum for a single Fellow or £900 per annum for a married Fellow, with allowances for travelling and other approved expenses. Further details and forms of application from the secretary, Medical Research Council, 38, Old Queen Street, London, S.W.1, with whom applications must be lodged by March 31.

Committee on Trial-case Lenses.—The Minister of Health has appointed a committee, under the chairmanship of Sir STEWART DUKE-ELDER, "to review standards for trial-case lenses and the method of measuring lens powers." Among the eight members are two other medical men, Mr. J. E. AVOUR, F.R.C.S., and Mr. F. W. LAW, F.R.C.S.

Journal on Viruses.—The forthcoming publication of a new journal, *Virology*, is announced by the Academic Press, New York. The aim of this journal will be to publish papers on the biological, biochemical, and biophysical aspects of the subject, with emphasis on the comparative approach. The new journal will fill an obvious gap in the literature. *Virology* will be edited by Dr. G. K. HIRST, of the Public Health Research Institute, New York, 9, and Dr. C. H. ANDREWES, F.R.S., of the National Institute for Medical Research, London, will be one of the associate editors. Volume 1, 1955, will comprise five issues, the first of which will appear in April. Annual subscription is $9.00, and the British agents are Academic Books Ltd., 129, Queensway, London, W.2.

Aircraft Seats.—Under new Air Navigation Regulations all new civil airliners imported into Australia after January 1, 1957, must have their passenger seats facing the rear of the aircraft. The Australian Director-General of Civil Aviation, Air Marshal Sir RICHARD WILLIAMS, is quoted as saying that such seats give three times the protection of forward-facing seats.

Lawrence Poole Prize.—The Edinburgh branch of the Infantile Paralysis Fellowship has given £1,020 to Edinburgh University for the founding of an annual, biennial, or triennial prize for work on the prevention of poliomyelitis or the treatment or rehabilitation of those suffering from it.

William Hyde Award.—Dr. ROGER BANNISTER has been chosen for this year's William Hyde Award by the Research Board for the Correlation of Medical Science and Physical Education. The award, valued at £300, was instituted by the Nuffield Provincial Hospitals Trust in memory of its first manager.

Lord Adrian, P.R.S., will receive the honorary degree of Doctor of Science of Hull University on July 19.

COMING EVENTS

British Council Courses on Anaesthesia and Plastic Surgery.—Courses for overseas specialists: "Anaesthesia," London, February 27–March 12; "Plastic Surgery," East Grinstead and London, April 17–30. Details from director, Courses Department, British Council, 65, Davies Street, London, W.1 (Tel.: Grosvenor 8011).

Radio.—"Crime Comics and the American Way of Life." Twenty-minute talk on the Third Programme by Irving Sarnoff, Ph.D., senior psychologist, Student Health Service, Michigan University, on Thursday, March 3, at 8.55 p.m.

Otology Lecture.—The first James Yearsley lecture, commemorating the founder of the Metropolitan Ear, Nose, and Throat Hospital, will be delivered by Mr. TERENCE CAWTHORNE at 5.30 p.m. on March 4 at Rushcliffe House, St. Mary Abbots Hospital, Marloes Road, Kensington, W.8. His subject will be "The surgery of the ear in the prevention and treatment of intracranial complications of chronic suppurative otitis media." The lecture will be open to the medical profession without fee.

Alcohol Symposium.—The Nutrition Society will hold a symposium on "Alcohol and its Nutritional Significance," at St. Mary's Hospital Medical School, on March 12. Details from Dr. R. J. L. ALLEN, c/o Monkhouse and Glasscock, Ltd., Snowfields, London, S.E.1.

All-India Obstetric and Gynaecological Congress.—The eighth congress will be held in Bombay from March 24 to 26. Further details from hon. secretaries, Purandare Griha, Chowpaty Sea Face, Bombay, 7.

A.N.Z.A.A.S., the Australian and New Zealand Association for the Advancement of Science, will hold its thirty-first meeting in Melbourne on August 17–24. Visitors from overseas will be welcome. Details from Professor J. R. A. MCMILLAN, Science House, 157, Gloucester Street, Sydney, Australia.

NEW ISSUES

Journal of Clinical Pathology.—The new issue (Vol. 8, No. 1) will be available next week. The contents include:

VISCERO-CUTANEOUS COLLAGENOSIS. Walter Pagel and C. S. Treip.
INTERSTITIAL PLASMACELLULAR PNEUMONIA DUE TO PNEUMOCYSTIS CARINII. H. S. Baar.
THE CELLS OF NORMAL HUMAN URINE. Philip Rofe.
A CASE OF CRYPTOCOCCAL MENINGITIS. D. C. Caldwell and S. S. Raphael.
NEEDLE NECROPSY. Richard Terry.
THE SPLEEN AND BLOOD EOSINOPENIA. Simon Sevitt.
THE USE OF A NEW CETRIMIDE PRODUCT IN A SELECTIVE MEDIUM FOR PSEUDOMONAS PYOCYANEA. E. J. L. Lowbury and A. G. Collins.
THE OCCURRENCE OF PASTEURELLA SEPTICA (SYN. MULTOCIDA) IN BRONCHIECTASIS. A. A. Cawson and J. M. Talbot.
THE FATE OF S. TYPHI IN BLOOD CLOT IN RELATION TO THE PROBLEM OF ISOLATION. Kenneth C. Watson.
EFFECT OF CHLORAMPHENICOL ON THE ISOLATION OF S. TYPHI FROM THE BLOOD STREAM. Kenneth C. Watson.
OPTOCHIN IN THE IDENTIFICATION OF STR. PNEUMONIAE. Eric F. Bowers and Leonard R. Jeffries.
THE ESTIMATION OF EVANS BLUE IN PLASMA. G. A. Bedwell, J. Patterson, and J. Swale.
THE EFFECT OF DIET UPON THE RESPONSE TO ORAL ANTICOAGULANTS. H. Payling Wright and M. Hayden.
BLOOD COPPER AND ITS RELATIONSHIP TO THE GLOBULINS. J. N. Cumings, H. J. Goodwin, and C. J. Earl.
ISOLATION AND EXAMINATION OF URINARY METABOLITES CONTAINING AN AROMATIC SYSTEM. C. E. Dalgliesh.
A SIMPLIFIED METHOD OF INVESTIGATING STEATORRHOEA. Dorothy Woodman and W. B. Yeoman.
A METHOD FOR THE DETERMINATION OF GLUTAMINE IN CEREBROSPINAL FLUID AND THE RESULTS IN HEPATIC COMA. T. P. Whitehead and S. R. F. Whittaker.
TECHNICAL METHOD: A SIMPLE METHOD FOR THE ESTIMATION OF PEPSIN IN GASTRIC JUICE. A. Wynn Williams.

Issued quarterly; annual subscription £2 2s.; single copy 12s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Friday, February 25

CAMBRIDGE MEDICAL SOCIETY.—At Addenbrooke's Hospital, 3 p.m., Miss M. Moore White: Infertility.

Monday, February 28

LEEDS UNIVERSITY.—At Littlewood Hall, General Infirmary at Leeds, 4 p.m., talk and demonstration by Sir Howard Florey, F.R.S.: Cinematographic Illustration of Some of the Phenomena of Inflammation.
MEDICAL SOCIETY OF LONDON.—8.30 p.m., discussion to be introduced by Mr. D. J. Browne and Mr. N. L. Eckhoff: Common Congenital Deformities.
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, 4.45 p.m., Dr. Joseph Needham, F.R.S.: New Light on Physico-chemical Aspects of Morphogenesis.

Tuesday, March 1

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. C. Hodges: Superficial *X*-ray Therapy.
OXFORD UNIVERSITY MEDICAL SOCIETY.—At Clarendon Laboratory, 8.15 p.m., Professor J. Rotblat, D.Sc., Ph.D.: Nuclear Physics and Medicine.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Theatre, 5 p.m., Mr. John Beattie: Abnormalities of Bladder Function.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., neurological demonstration by Dr. J. N. Milnes.

Wednesday, March 2

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: *Trichophyton rubrum* Infection.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—6 p.m., Dr. H. Engström (Stockholm): Anatomy of the Cochlea by the Electron Microscope.
INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. A. W. Badenoch: Haematuria.
LIVERPOOL MEDICAL INSTITUTION.—At Manchester University, 4.30 p.m., joint meeting with Manchester Medical Society, Professor A. W. Downie: Virus of Chickenpox and Herpes Zoster; Dr. C. A. Clarke: Some Methods of Investigating Inherited Factors in Disease.
MIDLAND MEDICAL SOCIETY.—At Birmingham Medical Institute, 154, Great Charles Street, 8.15 p.m., Dr. J. F. Brailsford: Lesions of the Intervertebral Disks.
ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE: EDINBURGH BRANCH.—At West Medical Theatre, Royal Infirmary, Edinburgh, 5 p.m., Dr. J. R. Innes: Defects in the Present-day Treatment of Leprosy.
ST. MARYLEBONE HOSPITAL FOR PSYCHIATRY AND CHILD GUIDANCE.—5.30 p.m., Dr. E. H. Larkin: Selection of Patients for Physical Treatment (with demonstration of treatment).

Thursday, March 3

●MOTHERS' CLINIC, 108, Whitfield Street, London, W.—2.30 p.m., Dr. Marie Stopes, D.Sc.: lecture and demonstration (on living models) on contraceptive technique.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.30 p.m., Otolaryngology Lecture by Mr. A. J. Gardham: Evolution of Major Surgery in the Mouth and Pharynx from the time of Trotter to the Present Day.
ROYAL EYE HOSPITAL.—5.30 p.m., Dr. T. H. Whittington: Some Aspects of Refraction Work: (2) The Reduced Eye and Retinoscopy.
ST. ANDREWS UNIVERSITY.—At Physiology Department, Medical School, Small's Wynd, Dundee, 5 p.m., Dr. F. G. Spear: Use and Misuse of Radiation.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. D. Curran: psychiatry demonstration.
ST. JOHN'S HOSPITAL DERMATOLOGICAL SOCIETY.—4.30 p.m., demonstration and discussion of clinical cases.
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, 4.45 p.m., Dr. S. R. Elsden: Respiratory Mechanisms in Bacteria

Friday, March 4

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. P. D. Samman: Lichen Planus.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., clinical demonstration by Dr. J. Smart: Lung Abscess.
LONDON UNIVERSITY.—At King's College, 5 p.m., Professor Jerome Hall: Mental Disease and Criminal Responsibility.
●LONDON UNIVERSITY.—At Queen Elizabeth College, 5.30 p.m., Professor J. A. C. Knox: Exercise and the Heart Rate.
METROPOLITAN EAR, NOSE, AND THROAT HOSPITAL.—At Rushcliffe House, St. Mary Abbots Hospital, 5.30 p.m., Inaugural Address by Mr. T. E. Cawthorne: Surgery of the Ear in the Prevention and Treatment of Intracranial Complications of Chronic Suppurative Otitis Media.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. R. W. Raven: Malignant Melanoma.
●ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW.—5 p.m., Mr. Matthew White: Thoracic Surgery in Children.
ROYAL INSTITUTION OF GREAT BRITAIN.—9 p.m., Sir Frederic Bartlett, F.R.S.: Thinking—An Experimental Approach.
ROYAL MEDICAL SOCIETY, Edinburgh.—8 p.m., Dissertation by Mr. A. McI. Smith: Some Aspects of General Practice.
ROYAL SANITARY INSTITUTE.—At Guildhall, Kingston-upon-Hull, 10 a.m., Mr. T. H. Jones, M.I.C.E.: Water Supply of Kingston-upon-Hull—Past, Present, and Future; Dr. W. Ferguson: Epidemiological Approach to Health Education.
WHIPPS CROSS HOSPITAL MEDICAL SOCIETY.—8.30 p.m., clinical meeting.

Saturday, March 5

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—12 noon, Dr. H. Engström (Stockholm): Anatomy of the Vestibule by the Electron Microscope.
MIDLAND TUBERCULOSIS SOCIETY.—At Birmingham Chest Clinic, 3 p.m., Dr. A. L. Cochrane: Epidemiology of Tuberculosis in the Rhondda Fach.

APPOINTMENTS

GREER, C. H., M.B., B.S., Pathologist, Victoria Eye and Ear Hospital, Melbourne, Australia.

INSTITUTE OF OPHTHALMOLOGY.—P. B. Schofield, M.R.C.S., L.R.C.P., Assistant Pathologist; C. M. H. Pedler, M.B., B.S. Junior Pathologist.

NORTH-EAST METROPOLITAN REGIONAL HOSPITAL BOARD.—Alexander Russell, M.D., M.R.C.P., D.P.H., D.C.H., Part-time Consultant Physician in Paediatric Endocrinology, Queen Elizabeth Hospital for Children; E. W. Emery, M.B., Ch.B., F.F.R., D.M.R.(T), Full- or Maximum Part-time Consultant Radiotherapist, North Middlesex Hospital and Annexes; K. A. D. Turk, M.D., Full-time Consultant Pathologist, Chelmsford Group of Hospitals; C. G. Nairn, M.B., Ch.B., F.R.C.S.Ed., M.R.C.O.G., Part-time Consultant Obstetrician and Gynaecologist, Prince of Wales's and Bearsted Memorial Hospitals; G. D. W. McKendrick, B.M., B.Ch., M.R.C.P., Part-time Consultant Physician in Infectious Diseases, St. Ann's General Hospital; A. S. Clark, M.B., B.S., D.P.M., Part-time Consultant Psychiatrist, Edmonton Child Guidance Clinic; J. H. P. Johnson, M.B., M.R.C.P., Full-time Consultant Chest Physician, Tottenham Chest Clinic; W. J. Jenkins, M.D., Full-time Consultant Pathologist and Medical Director, Brentwood Blood Transfusion Centre; J. P. S. Whitehead, M.R.C.S., L.R.C.P., Full-time Consultant Pathologist, Tilbury and South-east Essex Group of Hospitals.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Thomson.—On February 9, 1955, to Nancy S. M. Thomson (formerly Milne), M.B., Ch.B., wife of Thomas Nairn Thomson, B.Sc.(Econ.), B.Com., Ivybank, Blairgowrie, Perthshire, a son.

MARRIAGES

Phillips—Carp.—On February 22, 1955, at Toorak Synagogue, Melbourne, Australia, Leo Phillips, M.B., Ch.B., M.R.C.P., D.C.H., of Auckland, New Zealand, to Anne Carp, of Melbourne.

DEATHS

Johnston.—On January 28, 1955, at Old Court, Wellington, Somerset, Henry Stapleton Johnston, L.R.C.P.&S.I. & L.M., aged 71.
Low.—On January 24, 1955, in London, John Bruce Low, M.B., Ch.B., D.P.H., of 18, Causton Road, Highgate, London, N.
McIver.—On January 13, 1955, William John McIver, M.B., B.Ch., D.P.H., of The Demesne, Wistaston, Nantwich, Cheshire, aged 74.
Marsden.—On January 25, 1955, in London, Norman Spencer Marsden, M.B., Ch.B., Surgeon Commander, R.N.
Mayne.—On January 22, 1955, at "Caradon," Teignmouth, Devon, William Boxer Mayne, M.R.C.S., L.R.C.P.
Meehan.—On January 22, 1955, at "Maryfield," Duns, Berwickshire, Felix Patrick Meehan, M.M., M.B., Ch.B.
Moore.—On January 21, 1955, at 8, Groveley Road, Bournemouth, Hants, Edward James Fleetwood Moore, M.D.
Newton.—On January 27, 1955, at a nursing-home, Arthur Charles Duncan Newton, M.R.C.S., L.R.C.P.
North.—On January 15, 1955, at Axmansford Cottage, Ramsdell, Hants, Thomas North, M.D., F.R.C.S.I., late of New Southgate, London, N., aged 87.
Pooley.—On January 17, 1955, at Hill Rise, Dalton-in-Furness, Lancs, Edward Burdett Pooley, L.R.C.P.Ed., L.R.C.S.I. & L.M., aged 91.
Sheehan.—On January 25, 1955, at Norwich, Norfolk, William Joseph Sheehan, M.B., B.Ch.
Stalker.—On January 16, 1955, Alice Stalker, M.B., Ch.B., D.P.H., of Southport, Lancs.
Thompson.—On January 15, 1955, William Alexander Thompson, M.B., Ch.B., of 37, Derby Lane, Stoneycroft, Liverpool, Lancs, aged 33.
Walker.—On January 27, 1955, William Watson Walker, M.R.C.S., L.R.C.P., of 2, Chevening Road, London, N.W., aged 84.
White.—On January 21, 1955, at 187, Queen's Gate, London, S.W., John Duncan White, O.B.E., M.B., Ch.B., D.M.R.E.

Any Questions ?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Antibiotics and Buccal Ulceration

Q.—*What place have antibiotics in the treatment of stomatitis and buccal ulceration? If indicated, how should they be administered?*

A.—The answer, as to so many such questions, is that treatment depends on the cause. Antibiotics are worse than useless in *Candida (Monilia)* infection, and may indeed produce it. Penicillin is a specific for Vincent's infection. If there is some underlying condition (agranulocytosis or other blood disease and perhaps others less serious and less easily identified) antibacterial treatment of any kind, since it does not deal with the ultimate cause, may be unsuccessful. If the condition appears to be primary and not due to any resistant species such as *Candida albicans*, penicillin may be tried: none of the newer antibiotics has any special advantage for this purpose. When given in large doses parenterally (not less than 500,000 units daily of sodium penicillin: procaine penicillin does not produce sufficiently high blood levels) penicillin is excreted in the saliva, and this is perhaps the best way of giving it. Alternatively penicillin pastilles made with gelatin may be continuously sucked or penicillin chewing-gum used. Penicillin tablets (saccharose base) are unsatisfactory for prolonged use, and can in fact themselves produce a stomatitis.

Crepe Rubber Soles

Q.—*There is a current opinion among orthopaedic staff that the wearing of crepe rubber soles causes pains in the feet. Are there any facts ascertained concerning rubber footwear and the welfare of the feet?*

A.—It is a prevalent belief that crepe rubber soles are not suitable for children's feet. In fact, there seems to have been no investigation of this question at all. Certainly there can be no harmful effect on normal feet. In feet that are grossly abnormal there might be some complaint of pain, though I do not believe any harm would come from wearing such shoes. The reason that pain might occur is that a crepe sole does not give any rigid support to the foot. However, it is uncommon for children with foot abnormalities to complain of anything but minor pain. In short, I would say that crepe soles are quite suitable for shoes worn by children.

Alopecia Totalis

Q.—*A patient of mine, a man aged 43, has had total alopecia since childhood. He lost all his hair at the age of about 10; no illness is known to have been the cause of it. His hair then grew again and disappeared again each year until he was about 18 years old, since when he has been without hair on head or body. Every spring a few downy hairs appear on his face and scalp, but by mid-summer they have gone again. He is a reticent type of person, sensitive about his baldness. He wears a wig, but can you suggest any treatment for his condition?*

A.—Reports from the United States indicate that alopecia totalis may recover completely after systemic treatment with cortisone or A.C.T.H. It seems, however, that the baldness is likely to return very quickly once treatment is stopped, but perhaps this is not always so. The local application of cortisone and A.C.T.H. to the skin seems to be of no effect, but it may be hoped that hydrocortisone may prove successful in treating this condition. As yet, supplies of hydrocortisone in this country are not sufficient for the treatment of alopecia totalis, and its value is still uncertain. In any case, it is doubtful whether the disorder merits the hazards and expense of systemic steroid therapy. However, no other treatment is likely to be successful.

Obliteration of Tattoo Marks

Q.—*I have recently been consulted by a patient who is anxious to have some tattoo marks removed from his arm. They consist of three small initials, and have only been there for a few weeks. Is it possible to bleach them in any way or to lessen the intensity of the pigment? Apparently he is prepared to put up with a considerable amount of inconvenience.*

A.—The removal of tattoo marks, except by surgical excision and closure of the wound by a skin-graft or by suture, is not very satisfactory.

The only other method which has been seriously attempted is to use a tattooing machine to drive an escharotic, such as tannic acid, into the skin over the tattoo mark. This causes necrosis of the skin and healing by scar tissue. It therefore leaves an outline of the previous tattoo mark as a scar. It does, however, achieve the removal of the coloured dyes.

Anaemia in Pregnancy

Q.—*I should be grateful for information on the treatment of the pregnant woman whose routine haemoglobin estimation at a local authority antenatal clinic is about 60% to 80%.*

A.—Although it has recently been disputed, the general view is that the physiological hydraemia of pregnancy results in an apparent anaemia and that a haemoglobin reading of 80% (11.0 g. per 100 ml.) or more is normal for the latter part of pregnancy. If anaemia is present, and if it is the result of an iron deficiency, treatment should be by modification of the diet and, if need be, by the oral administration of iron in the form of ferrous sulphate, ferrous carbonate, ferrous gluconate, iron and ammonium citrate, or proprietary preparations of colloidal iron. While it is true that one or other of these preparations may cause constipation or diarrhoea in certain women, this can only be determined by giving each a trial.

Failure of hypochromic anaemia to respond to oral iron therapy is sometimes explained by achlorhydria, which is not uncommon during pregnancy, so hydrochloric acid may be administered in addition to iron. If this fails, there is a clear indication for reference of the patient from a district antenatal clinic to the nearest hospital where full investigation can be carried out to establish the type of anaemia present, and where further treatment can be arranged or advised according to the findings.

Oversexed Women

Q.—*Is there any reliable medical treatment—for example, hormones or sedatives—to lessen the sexual urge in women?*

A.—It is worth trying the effect of ethisterone, 5 mg. three times a day. This is an expensive remedy, but it has been known to have the desired effect. Alternatively, small doses of bromide or phenobarbitone thrice daily are effective in some women, as is shown by the fact that some epileptic females cannot reach orgasm as long as they continue with sedation. Sensible advice about behaviour, masturbation, and the avoidance of alcohol would doubtless also help. With regard to masturbation, many children are brought up to believe that any self-relief is an unforgivable sin, and the punishment for it will be diseases of the sexual organs or damage to childbearing capacities. In fact, there seems no reason to consider masturbation as anything but normal in the celibate adult. Of Kinsey's figures from about 5,000 males 96% had masturbated and some 62% of his series of women. There seems to be no valid reason for fearing that a habit will become established: in normal people masturbation is only resorted to in the absence of more satisfactory outlets: certainly for many relief obtained in this

way would seem preferable to making a whole-time effort to repress desire as some young people have to do. A little kindly reassurance from the doctor may bring great relief along these lines. Admittedly the question is a complex one, but such advice would probably be given by most present-day psychiatrists.

Dental Anaesthesia for Children

Q.—*I am often asked by our local dentists to administer a domiciliary anaesthetic to children (3 years and upwards) for the extraction of a varying number of teeth, from two to a total clearance. It is seldom that one can avoid an open fire, especially in winter. What is the best anaesthetic agent to use? On a recent refresher course for general practitioners which I attended hands were raised in horror at the mere suggestion of chloroform, but no alternative (except ethyl chloride and ether) could be suggested. What is your expert's advice?*

A.—The choice of dental anaesthetic for infants and young children varies from single-dose ethyl chloride or divinyl ether for the simplest extraction, to endotracheal anaesthesia with nitrous oxide and oxygen with an adjuvant for the longest operations. The latter would be quite unsuitable in domiciliary practice. Nasal nitrous oxide and oxygen alone is a difficult anaesthetic to give to the very young without some premedication, and on the whole is not advised for the occasional anaesthetist. Ether, ethyl chloride, and divinyl ether are all inflammable and explosive, particularly so in the presence of oxygen or nitrous oxide. They should not be administered in the presence of an open fire. Chloroform is inadmissible because of its special pharmacological dangers, now too well documented to need repetition and out of all proportion to the nature of this operation.

The practical outcome is that unless the anaesthetic can be administered in a room without an open fire or for that matter any other source of ignition, it should not be administered at all. A larger question is whether dental extractions under general anaesthesia should be performed in a patient's home. If the reasons for doing so seem sufficient, any fire should be extinguished and any source of ignition removed from the room before the anaesthetic is administered. Quite apart from the explosion risk, the difficulty of avoiding and treating the by no means rare anaesthetic hazards of overdose, inhalation of vomit, and respiratory obstruction in a private house is very great. The death of a child in these circumstances would be difficult to excuse merely on grounds of expediency.

Paradichlorobenzene

Q.—*A patient sleeps in a room with little ventilation and with wardrobes and drawers so generously treated with paradichlorobenzene that the atmosphere seems constantly charged with it. Is this dangerous, or might it account for vague symptoms otherwise reasonably attributable to advancing years, or for a mild irritating cough?*

A.—Paradichlorobenzene is not usually considered to be a particularly toxic substance, though it is a narcotic and a liver poison. Inhalation of vapour is said to lead to headache, dizziness, and vomiting in sensitive people. I have been able to find only one reference in the literature to occupational poisoning among those handling the material. Wallgren[1] has recently reported poisoning in eight workers producing it. The symptoms were loss of appetite and weight and irritation of the eyes and throat. There were also increased reflexes, fine finger tremors, and some degree of methaemoglobinaemia. More serious, however, is a single report[2] of two women both excessively exposed at home who developed cataract after an attack of jaundice a year previously. The significance of these observations might be questioned in view of the widespread use of paradichlorobenzene, but in any case a reduction of the hazard should be relatively easy to achieve.

REFERENCES

1 *Zbl. ArbMed. ArbSchutz.*, 1953, 3, 14.
2 Berliner, M. L., *Arch. Ophthal.*, 1939, 22, 1023.

Magnesium

Q.—*What is known about the magnesium requirements of man? Does deficiency or excess of this element lead to any ill-effects and, if so, what?*

A.—The usual dietary intake of magnesium is 0.2 to 0.6 g. (15–50 mEq) daily. The minimal requirement of magnesium in man is not known with any accuracy. In animals, deprivation of magnesium has been shown to cause tetany associated with low serum levels of magnesium. In man, the absence of a normal diet during prolonged parenteral feeding has been shown to lead to low serum levels of magnesium; the tremor in delirium tremens has been attributed to magnesium deficiency induced by anorexia, and low values of serum magnesium have been associated with it. Although magnesium is present in a considerable amount in cells, the effects of a cellular deficiency of magnesium in man are not known. High serum levels of magnesium can lead to stupor and coma. Magnesium in the diet could scarcely be adequate to produce this effect, but the giving of magnesium salts to patients with renal failure may elevate the serum level and so accentuate drowsiness.

NOTES AND COMMENTS

Lepers in Revolt.—Dr. M. G. CORCOS (Trinidad, B.W.I.) writes: "In your number of January 15, on p. 175, under 'Medical News' appears the paragraph headed 'Lepers in Revolt,' in which you correctly quote newspaper reports concerning myself. The incident did in fact occur, and has been followed by a considerable amount of publicity in both the world press and in the local press, most of it unfortunately highly favourable to me. I would be very grateful, therefore, if in fairness to me you could see your way to publishing the following disclaimer:

"Subsequently to January 7, 1955, a number of articles, letters, and reports have been appearing in the lay press, some purporting to give my views and practices in the treatment of leprosy patients and in leprosy control, and some including statements by patients and other persons lauding me, my views, and my actions. Please note that none of the articles, letters, and reports purporting to give my views and practices has been or will be published with my written, spoken, or implied consent. Many of the views and practices are not necessarily my own, and are in any case held and practised by a large number of medical practitioners, nurses, and medical auxiliaries throughout the world, as well as by various bodies interested in leprosy and leprosy control, including the World Health Organization. The laudatory statements, articles, letters, and reports by patients and others have been, and will be, in no way solicited by me, and have been, and will be, published without my written, spoken, or implied consent."

Burns from Petroleum Bitumen and Paraffin Wax.—Arising from the reply to the question on the treatment of pitch and tar burns ("Any Questions?" November 27, 1954, p. 1306), it has been asked whether the same treatment would be applicable to burns from petroleum bitumen and paraffin wax. OUR EXPERT replies that the treatment described is equally suitable for these types of burn.

Technique of Artificial Insemination.—Dr. JOAN MALLESON (London, N.W.1) writes: There is a slight error in the reference to the use of the insemination syringe ("Any Questions?" January 29, p. 301). Any apparatus such as this, dealing with sperms, should be washed in plain water and dried in air. A sediment of soap is most detrimental to sperm life. The syringe and glass vessel also need warming, in the axilla, to blood heat, for cold glass is a shock to spermatozoa. Full details of the use of the syringe have been published.[1]

REFERENCE

1 *Practitioner*, 1952, 169, 161.

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